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The Evolution and Dynamics of the Sectoral System of Innovation – A Case Study of Orphan Drug Innovation in the US

Jin Ding

Declaration

I declare that this thesis was composed by myself, that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or professional qualification.

July 2017

Jin Ding

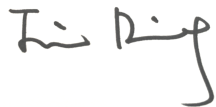
A handwritten signature in black ink, appearing to read "Jin Ding". The signature is written in a cursive style with a long, sweeping underline.

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Abstract

Drugs for treating rare diseases had been neglected by the pharmaceutical industry for a long time, due to the complex and costly drug R&D process as well as a small unprofitable market. Since its introduction in 1983, the Orphan Drug Act (ODA) has sought to prompt the innovation of drugs for minority diseases by reducing the regulatory and economic barriers. The incentives of the ODA have been effected through market protection, tax credit, fee waiver and grants to increase the accessibility of orphan products for the public. The number of orphan drugs available in the market has risen sharply from just ten in the decade before 1983 to over 400 since 1983. This increase implies a substantial improvement of the healthcare of patients suffering rare diseases and a success of the orphan drug legislation with the aim to motivate the development and manufacture of products that have low commercial potentials. Although it is evident that the ODA has successfully stimulated drug companies to develop numerous orphan products, treatments are very expensive. The sales of blockbuster orphan drugs have provided drug companies with unusually high-profit margins and limited patient access to treatments. The dilemma presented by the ODA reflects many of the issues currently faced by policymakers.

In this thesis, we have analyzed the long-term evolution of the bio-pharmaceutical industry. In particular, we have examined drug discovery in the period of random screening, rational design and network collaboration, and explored the influence of the ODA. We have taken the theory of the sectoral system of innovation, and combined it with the complex adaptive model of innovation, and found that the complex version of that theory is capable of explaining the comprehensive drug innovation system.

A Multi-agent Based Model has been introduced to identify and analyze the dynamics of bio-pharmaceutical innovation. The model has explored the roles of the main players in the sector and the influence of their relationships embedded

in the process of orphan drug innovation. Through this model, we have investigated the mechanisms of how the incentives stimulate orphan drug innovation during the period from 1983- 2012. Moreover, the model has been applied to solve the dilemma of the ODA through analyzing how to achieve the best trade-off between orphan drug developments.

Drawing upon the results of the simulation, we provide a sound basis for adjusting the ODA incentives to strikes an appropriate balance between stimulating orphan drug innovation and providing benefits to society, propose some resolutions to the ODA, while also to motivate orphan drug development in a financial way. The Advice for other countries planning to enact the orphan drug legislation and directions for further research suggested by this model have been put forward.

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List of Abbreviations

ABM	Agent-based Model
ABST	Agent-based Software Toolkits
BLA	Biologics License Application
CAS	Complex Adaptive System
CDER	Center for Drug Evaluation and Research
DMCC	Data Management and Coordinating Center
ENL	Erythema Nodosum Leprosum
FDA	Food and Drug Administration
GAs	Genetic Algorithms
HFM	History-friendly model
NCATS	National Centre for Advancing Translational Sciences
NDA	New Drug Application
NIH	National Institutes of Health
NME	New molecular entity
NORD	National Organization for Rare Disorders
NSI	National System of Innovation
ODA	Orphan Drug Act
OOP	Object-Oriented Programming
OOPD	Office of Orphan Products Development
ORDR	Office of Rare Disease Research
PDUFA	Prescription Drug User Fee Act
PHS	Public Health Service
RDCRC	Rare Diseases Clinical Research Consortia
RDCRN	Rare Diseases Clinical Research Network

RSI	Regional System of Innovation
SI	System of innovation
SSI	Sectoral System of Innovation
UCD	Urea Cycle Disorders

Chapter 1 Introduction

The growth of the pharmaceutical industry has slowed down in the last decade due to patent expiration, generic competition, drying pipelines and the increasingly strict regulatory guidelines. In addition, the economic environment alongside the influences of regulatory and productivity challenges has made the pharmaceutical industry struggle to develop innovative drugs at low costs.

In such a situation, there has been a significant increase in the innovation of a specific type of drugs since the 1980s, and many biotechnology companies have been founded to develop these drugs and successfully market them. These specific drugs now account for over 40% of the new FDA-approved drugs (Jenkins 2016). In contrast, only ten drugs were developed by the industry in the decade before 1983 (NORD 2013). This special type of drug is known as the orphan drug. It is distinct from other ordinary drugs because it is used to treat diseases affecting a patient population below 200,000 in the United States. Due to the particularly small market resulting from the low prevalence, most drug companies did not invest in orphan drugs before the 1980s.

The significant increase in orphan drug innovation after 1983 was due to a breakthrough in the orphan drug legislation. The enactment of the Orphan Drug Act (ODA) in 1983 denotes the landmark act shifting the orphan drug R&D from depression to prosperity. By offering market exclusivity, tax credit, assistance and grants for drug development, the ODA has productively motivated drug companies to address the need for patients with the rare disease. In the 30 years after 1983, more than 400 orphan drugs have been approved in the US. In 2015, orphan drugs accounted for approximately 18% of global prescription sales, and this is projected to increase to 20.2% in 2020 (Hadjivasiliou 2015). Through the rapid increase in the sales of orphan drugs, the ODA has brought remarkable growth to the biotechnology industry (Goodman 2010).

The ODA is recognized as one of the most successful legislative actions in the US in recent times (Haffner 2006). However, despite its success over the last 30 years, the ODA has been criticized for its 7-year market exclusivity that leads to the high price of orphan drugs. Currently, ‘orphans’ are no longer ignored by drug companies; instead, they are the golden opportunity that companies scramble to grasp.

This chapter consists of three sections. The first section contains a brief introduction to the pharmaceutical industry, including the opportunities and challenges faced by the sector. The second section concentrates on the ODA and its influence, including its incentives; the current situation of orphan drug innovation; and the achievements and limitations of the ODA. The third section introduces the research questions, objectives and structure of this thesis.

1.1 Pharmaceutical Industry

The pharmaceutical industry has faced extraordinary challenges in the last several years, although it has been very successful in creating a stream of novel drugs with significant therapeutic benefits. The industry underwent a wide range of unprecedented changes, such as massive losses from patent expirations, high-cost pressure, declining productivity and enormous uncertainties from regulatory regimes (Kola and Landis 2004, Hendry and Brown 2005). At the same time, significant advances in biotechnology and genomics, venture capital investments pouring in, close collaborations among the university, biotechnology company and Big Pharma paved the way for the emerging biopharmaceutical industry.

1.1.1 The Opportunities of Bio-Pharmaceutical Industry

The pharmaceutical industry is an extremely profitable sector in the US economy (Henry and Lexchin 2002). According to the 2016 Global 500, Johnson

& Johnson was ranked 103rd with a total revenue of US\$ 70.074 billion but with a profit of US\$ 15.409 billions, compared with Wal-Mart ranked 1st with a total revenues of US\$ 482.130 billion and a profit of US\$14.694 billion. There were 12 pharmaceutical companies in the fortune 500 list, and eight of them were ranked in the top 50 profitable companies in 2010.

In 1980, the Bayh-Dole Act was adopted. It allows agencies to patent discoveries from government-funded research and to license these patents for commercial use. This has successfully narrowed the gap between fundamental research and commercial applications by facilitating the transfer of knowledge from universities and non-profit research institutions to the industry. Since then, drug discovery has become more dependent on basic research, and its practical payoffs have motivated universities to obtain patents. This approach ensures that the outcomes of basic research are applied for commercial purposes more quickly and easily (Rai and Eisenberg 2003).

The development of science and technology, especially the rapid advance of biochemical and genetic processes, boosted the growth of discovery and development of various medical products, especially biotechnology drugs (Rohde 2000, Haffner, Whitley et al. 2002). The type of biotechnology drugs is diverse and includes new molecular entities such as recombinant-DNA product; older drugs with new medical uses; and bioactive molecules such as enzymes, antibodies and tissue-engineered products. The diversity of orphan drugs is reflected by the range of conditions targeted such as cancer, cystic fibrosis, renal disease, rheumatoid arthritis and cardiovascular disease. The development of these drugs have enhanced patients' quality of life and generated significant revenue for the industry.

The impact of orphan drugs on health care can be seen in two aspects. On one hand, this is the first instance that an innovation in biotechnology has directly resulted in clinical success in rare conditions such as multiple sclerosis, hepatitis, renal disease, and Gaucher disease. On the other hand, the same

innovations have significantly enhanced therapies already existing for more prevalent conditions such as Hepatitis B.

Biotechnology has also contributed to other sectors by creating many job opportunities and subsequently revenue for the companies. Public research organizations have developed a close relationship with the biotechnology industry for developing and marketing their inventions. A vast majority of the biotechnology firms started by licensing the promising work done in the laboratory settings. The close relationship improves the knowledge transfer between academic institutions and industry.

In short, the vibrancy of biotechnology has had a significant impact on the healthcare system including academic research, pharmaceutical industry and patients. The impact of the new technology on the pharmaceutical sector is significant and far-reaching.

1.1.2 The Challenges of Bio-Pharmaceutical Industry

Despite new technologies and approaches, the number of organic drugs has not increased, while the cost and time for drug development has not decreased as expected.

Depressing Productivity

The R&D productivity has been declining for many years (Paul, Mytelka et al. 2010). Although the number of newly approved drugs by FDA hit a 15-year high in 2012, the average number of orphan drugs was just 33.8 in the ten years from 1993 to 2002, and 26.3 during 2003 to 2012 (Figure 1). The lower rate of FDA new drug approval could be attributed to the following: drug research targeting more complex diseases such as cancer; the entry bar for the new drugs is higher than before; and the regulations are more demanding for drug approval.

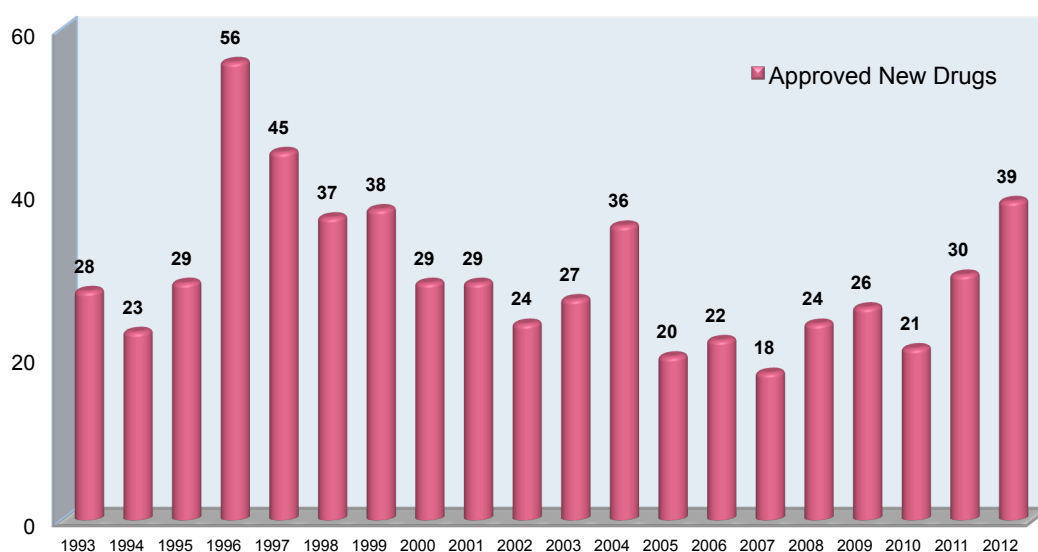


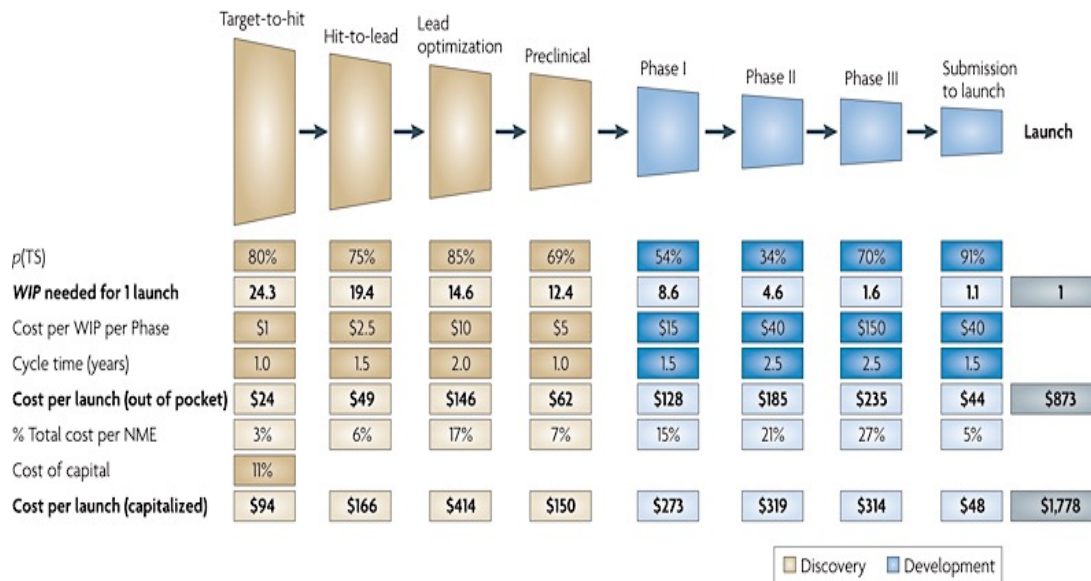
Figure 1 The Annual FDA Approvals from 1993 to 2012

A number of drug patents are at risk of expiration in upcoming years, and this will lead to generic competition and price decline. As a result, Big Pharma is would like to refill their pipelines. Moreover, orphan drugs account for a small percentage of the approved new drugs, with 21 drugs approved by FDA in 2008; and 24 drugs approved in 2009, but ‘first-in-class’ drugs decreased from 29% to 17% (Paul, Mytelka et al. 2010). Therefore, improving productivity, especially developing the revenue-generating medicines (innovative drug or the first-in-class drug), is regarded as the biggest challenge for the pharmaceutical industry.

Increasing R&D Costs

Drug discovery and development is a costly and time-consuming innovation process. According to Figure 2, the R&D of an approved drug takes 13.5 years and costs \$1,778 million on average. The cost of new biopharmaceutical products is approximately \$198 million in the preclinical phase and \$361 million at the clinical stage. Adding the cost of time, the numbers increase to \$615 million and \$626 million, with the total cost coming to \$1241 million for pre-clinical and clinical trials (DiMasi and Grabowski 2007). Drug companies

need to recoup the increasing R&D cost via the sale of the drug and make profit to maintain its sustainable development.



(Source: Paul et al., 2010)

Figure 2 The process of drug discovery and development¹

The stringent regulatory environment, higher attrition rate, increasing difficulty of drug discovery and the pursuit of more difficult therapeutic goals lead to the high costs of drug development (DiMasi, Hansen et al. 2003, Dickson and Gagnon 2004). Admittedly, patients and government will spend more money on the healthcare.

Accessing to Capital

Biotechnology companies have faced an increasing number of challenges to access sufficient capital in the resource-constrained realities. Venture capitalists, public investors, and alliances with big pharmaceutical companies are the three principal sources biotechnology firms heavily relied on. The

¹ The model shows the stages of drug discovery and development from laboratory to market. The model is built on the industry data and describes the performance of each R&D process. The main indicators include: $p(TS)$ means the probability of successful transition from one stage to the next, WIP means the number candidates needed in each stage to achieve one approved product in the end, the time and cost of each stages.

global economic crisis froze the path to capital that is the lifeline for the research-intensive industry like biotechnology industry. Venture capitalists, public investors and big pharmaceutical companies have become increasingly selective to choose the object of investment since then.

Demanding Regulation Environment

The process of drug discovery and development is significantly influenced legislation. The United States Federal Food, Drug and Cosmetic Act (FFDCA) of 1938 gave the authority to FDA to oversee the safety of food, drugs and cosmetics. Manufacturers were required to provide evidence to demonstrate that drugs are safe. With the aim of protecting the public health from wasting money and endangering their health on ineffective medicines, in 1962, the Kefauver Harris Amendment (K-H amendment) also required companies to provide proof of both the effectiveness and safety of their products for FDA approval review. The K-H amendment necessitated that drug companies demonstrate that new drugs are both safe and effective based on the three-stage clinical trial data. These two acts exert their influence on drug R&D in two ways: firstly, sponsors have to provide evidence of not only safety but also effectiveness; and secondly, the FDA is responsible for reviewing the data and grant approval to qualified drugs.

During the period from late 1960s to 1970, the enactment of K-H Amendment made the development process at least two years longer, which increased R&D costs from \$4.7 to an estimated \$54 million (Asbury 1992). Even with the protection from Bayh-Dole Act, because making profits is the ultimate goal of pharmaceutical industry, products with little prospect of commercial return had been neglected by the industry. For instance, drugs treating rare disease generally indicated a relatively low return from the sales on the R&D investment, so these drugs were scarce in the market before the 1980s.

The average cost of new biological agents for cancer and other rare life-threatening diseases has increased annually (Maggon 2005). With the ever-

rising healthcare expenditure, the government has to manage tremendous fiscal pressure amidst budget deficits balloon and unemployment. The potential returns on the pipeline will be affected by increased rebate. As the patents of blockbuster drugs are scheduled to go off patent in these years, the revenue and cash flow will inevitably reduce. Only the most innovative and affordable drugs can meet the demand of the government. It is critical for drug companies to control their costs as well as improve R&D productivity, collaborate more extensively and maintain a close relationship with the regulators.

1.1.3 The Orphan Drug Innovation before the ODA

Drug companies usually focused on the markets that offer the substantial return on investment, such as chronic disease with a high prevalence. In contrast, drug companies were unwilling to develop the unprofitable drugs that affect very few populations. Historically, healthcare system and drug companies did not pay attention to the needs of patients with rare diseases. Under this unique circumstance, the commercial interests of the industry and the public health of the patients suffering from rare diseases coincided.

Besides the small market, the R&D of orphan drugs faces other difficulties. Firstly, the market for these drugs was so small that drug companies cannot recoup the costs of drug discovery and development. Secondly, the small sample size of studies made it difficult to design effective clinical trials for drug approval. Finally, most orphan drugs were not eligible for the patent protection, so other companies could manufacture and sell the same drug. This competition would decrease profitability and exacerbate the difficulty of recovering costs.

1.2 The Advent of the ODA and the Performance of Orphan Drug

Although an individual rare disease affects a relatively small cohort, approximately 30 million Americans are affected altogether. With advocacy efforts of National Organization for Rare Disorders (NORD), in 1983, President Ronald Reagan signed the ODA into the legislation of United States for the creation of incentives to change the situation. In addition, the ODA symbolizes a triumph of patient advocacy collaborating with government, public media and other supporters to address the critical unmet medical need of patients with rare diseases.

1.2.1 The Advent of the ODA

The public awareness of rare diseases had increased in the 1970s. Although they are not very prevalent, over 30 million Americans suffer from about 7000 rare diseases. Hence, the healthcare of patients with rare diseases should be handled with the same priority as other patients regardless of commercial interests. Patient advocacy groups had played a significant role in promoting the orphan drug legislation. In 1983, the ODA emerged from the influences of various factors including technological advances, public and congressional concern, regulatory and industrial entities in the United States (Asbury 1992).

The Orphan Drug Act provides three major incentives. The first is offering a seven-year period of market exclusivity to the sponsors with approved orphan products. The seven-year market exclusivity is only authorized for the drug treating the rare disease. Secondly, the act provides tax credit to cover half of the costs of clinical trials. Since the remaining 50% of the costs are deductible, the total reduction in tax liability is 73% (Asbury 1992). Thirdly, the act authorized Orphan Products Grants Program administered by the FDA to fund the clinical trials of promising orphan products. The Orphan Products Grants Program is FDA's largest grants program with an annual budget of US\$14 million currently. Since 1983 FDA has provided more than \$290 million for over

500 grants for research on rare diseases, and over 45 approved products were partly funded by the grants (Needleman 2012). In 1997, Congress created an additional incentive that provided exemption from the drug application user fee of at least \$500,000 charged by FDA (OIG 2001). Some of the sponsors can also take advantage of the fast review for their applications if their products are developed for treating life-threatening illness without treatment on the market at the time of application.

Orphan drugs have to experience the same development process as non-orphan drugs to meet the same standards of effectiveness and safety. Indeed, as the result of a small number of patients available to be enrolled in the clinical trial, the drug can only be tested in a very small population. FDA and patient advocacy groups provide various assistance to help the sponsors design and organize clinical trials, and solve the problems emerging in the trials. Using an extreme example, the orphan drug approved with the smallest scale of the clinical test is bovine pegademase (Adagen) treating Severe Combined Immunodeficiency Syndrome (SCID) (Haffner 2006). The clinical trial for this involved only eight patients, since there were only 14 patients afflicted with this rare disease in the US at that time. Nevertheless, because all of the patients benefited from this drug, it attained FDA approval. Hence, FDA and the patient group played an important role in the approval of Adagen.

1.2.2 The Performance of Orphan Drug Innovation

The ODA has unquestionably stimulated the development of orphan drugs and successfully brought forth drugs for the rare disease in unprecedented number and given hope to millions of patients. During last 30 years, there is a significant improvement of orphan drug R&D (Figure 3). The number of approved orphan drugs increased dramatically from 2 in 1983 to 25 in 2012.

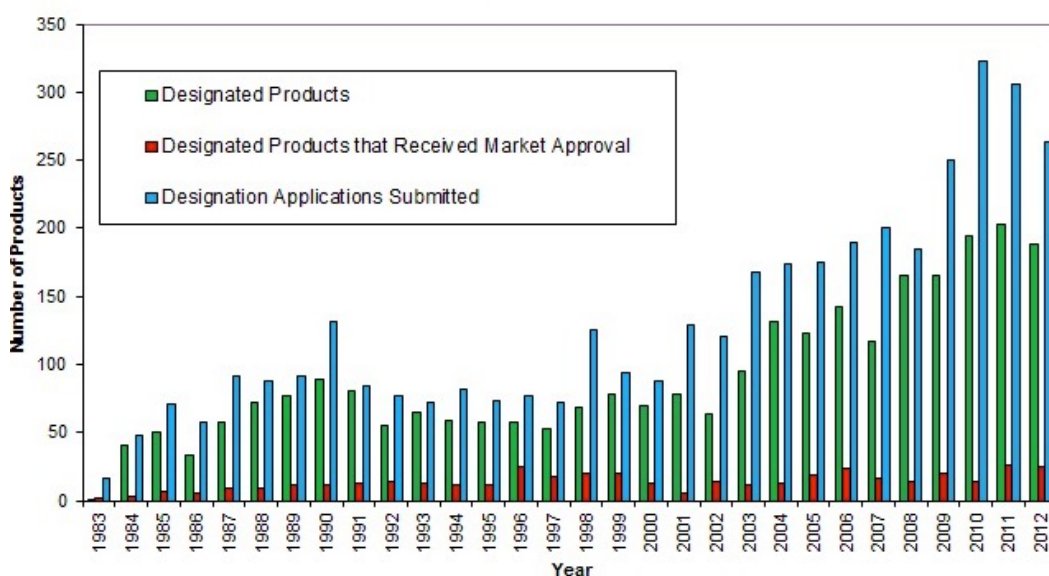


Figure 3 The Orphan Drug Application from 1983 to 2012

The Explosion of Orphan Drugs

In the 25th anniversary of the US Orphan Drug Act in 2008, it was estimated that over 17 million people had benefited from orphan drugs in the US. Nowadays, orphan drugs account for an increasing percentage of all new FDA-drug approvals. In 2015, about 47% of the approved novel drugs (21 of 45) were used to treat rare diseases.

20% of orphan designations are innovative biotechnology products stimulated by incentives of the ODA. In addition, approximately 50% of all the biological products with the FDA market approval in the US have orphan status from 1983. The categories of these biological products are diverse, and include therapeutic and diagnostic monoclonal antibodies, cell therapy, gene therapy, enzyme-replacement therapy for metabolic disorders and novel drug delivery biomolecules (Haffner, Whitley et al. 2002).

Several factors have contributed to propelling the development of these biological orphan products. The first one is the nature of the rare disease. Since rare diseases are generally serious and life-threatening conditions with limited treatment options, drug companies have to try the latest technology as other

known approaches fail. Since most rare diseases are generic, discovering treatment for them needs to rely on biotechnology. The second factor is the financial incentives of the ODA, which provides grants for drug development, tax credit of clinical test, fee reduction of drug approval and market exclusivity for drug marketing. These financial incentives reduce the high pressure of finance and risk; as a result, manufacturers are more likely to invest in orphan drug innovation.

The ODA not only benefits the patients affected by the rare disease but also benefits neglected diseases. Many of the drugs used to treat neglected diseases in the developing countries also qualify as orphan drugs in the US, since many neglected diseases in developing countries affect less than 200,000 persons in the US (Goodman 2010). Besides, the basic and clinical research on rare disease not only facilitates orphan drug R&D but also improve our understanding of the pathophysiology of other common diseases. In sum, the knowledge generated from orphan drug R&D also holds relevance for R&D of other non-orphan drugs.

The Boom of Biotechnology Company

The ODA has a significant economic influence on the growth of the biotechnology industry (Haffner 2003). The development of recombinant DNA technology in 1970s led to the subsequent creation of several biotechnology companies till the early 1980s. These companies focused on rare diseases and developed novel drugs for them. For example, the first marketed products of Genentech, Amgen and Genzyme Corporation as well as most US biotechnology companies are orphan drugs (WÄStfelt, Fadeel et al. 2006). Orphan indications have become the target of biotechnology companies (Mullard 2013). The favorable regulatory environment such as accelerated approvals, priority reviews and the ODA make the US the most attractive place for start-up biotechnology companies (Faden and Kaitin 2008).

1.2.3 The System of Orphan Drug Innovation

The innovation system of the orphan drug involves the sharing of resources among various organizations. To reduce the cost and expedite the progress, the orphan drug innovation system has established an active collaboration with a wide range of public and private organizations, including research organizations, government agencies, advocacy groups, biotechnology companies and pharmaceutical companies. This system has also built an effective mechanism for sharing research resources and infrastructures to take full advantage of the limited funding, expertise, and information.

Drug companies

Drug companies have used various models to achieve higher productivity by sharing costs and risk. On one hand, most sponsors are small- to medium-sized firms, with many focusing only on orphan drugs (Needleman 2012). Biotechnology companies share the costs and findings of early-stage rare disease research with research organizations and share the expertise and marketing resources with pharmaceutical companies during the late-stage drug development and commercialization. On the other hand, the collaboration among drug companies, advocacy groups, and government agencies has contributed a lot to the design of the clinical trial to satisfy FDA criteria. Although the development of orphan drugs may yield fewer trials and less money, clinical trials for orphan drugs is limited by the small sample size and distribution of trial population. In order to enroll a sufficient number of rare disease patients, Office of Rare Disease (ORD) provides support for the clinical research and assists patient advocacy groups; FDA offers flexibility for addressing the medical needs of the patients while meeting the safety and efficacy standards.

Patient Groups

Rare diseases had been neglected for a long time, and the morbidity of the illness had created a negative impact on patients with rare diseases. In

response, patient groups have attempted to improve their physical, emotional and financial conditions by providing funding, policy-making, and offering support for the research process. The largest patient advocacy group, NORD, provides an important platform for research organizations, drug companies, patients and policy-makers to accelerate the innovation of orphan drug. The number of advocacy groups keeps increasing, which not only reinforces the public awareness towards rare disease and strives for the improvement of patients' healthcare but also promotes and funds the drug innovation.

Authorities

The orphan drug is the most rapidly expanding area of drug innovation, but it is also the most challenging area to administrate. Due to the small number of patients, FDA provides flexible approaches to establishing safety and effectiveness standards. FDA introduces regulations, such as Fast Track, Priority Review, and Accelerated Approval, aiming at speeding the approval process for novel medicines; these approaches ensure that patients get the treatments as soon as possible. Despite the fact that the orphan drug should meet the same requirements of safety and efficacy, it seems easier to complete the data collection and analysis in the case of running a clinical trial with the small size of patient population than conducting trials involving several thousands of patients.

In all, the orphan drug innovation system is a complex adaptive system with many players interacting with each other to adapt to the changing technology and regulation environment.

1.2.4 The Influence Around the World

The Orphan Drug Act was so successful at stimulating drug innovation in the US that its influence had spread to other countries, including Singapore in 1991, Japan in 1993 and Australia in 1997. These countries also successfully

introduced legislation to encourage drug development for rare diseases. The European Union (EU) passed orphan drug regulation in 1999. The EU orphan drug regulation is similar to the US Orphan Drug Act, and provides six main incentives for drug companies to bear the high cost and risk of orphan drug development.

Two studies have compared the performance of the European Medicines Agency (EMA) and the FDA. The first study showed that the number of approvals between 2000 to 2005 was three times higher in the US than in the EU (Faden and Kaitin 2008). The second study assessing the products approved in 2008 found that about 39% of the new orphan drugs were approved by the FDA, 28% were approved by the EMA and 33% were approved by both of them (Graham 2010). There is no doubt that the US is the most successful place for stimulating orphan drug innovation worldwide. However, some orphan drugs “have been approved and available in EU, but not in the US, and vice versa (Sardana, Zhu et al. 2011)”. In the current regulatory climate, collaboration among regulatory agencies is necessary. EMA and FDA jointly signed a Confidentiality Arrangement, which facilitates the information sharing about the legislation, medical products, and clinical reports.

1.3 The Challenges of the Orphan Drug Act

Although the ODA has successfully generated many orphan products to treat rare diseases, “the success of the Act in terms of the numbers of products developed tells only part of the story (Rohde 2000)”.

There are still a large number of rare diseases without effective treatment, and some of the approved orphan drugs are sold at a very high price. Although rare diseases are diverse, most of the orphan designations are authorized for the treatment of certain serious or life-threatening diseases, while a large number

of rare diseases are neglected by the industry. As shown in Figure 4, trends that emerged over the past decades indicate that the highest percentage of approved orphan drugs (38) is used to treat the rare forms of cancer, for example, ovarian cancer or hairy-cell leukaemia, followed by metabolic disorders that are the second largest group of approval.

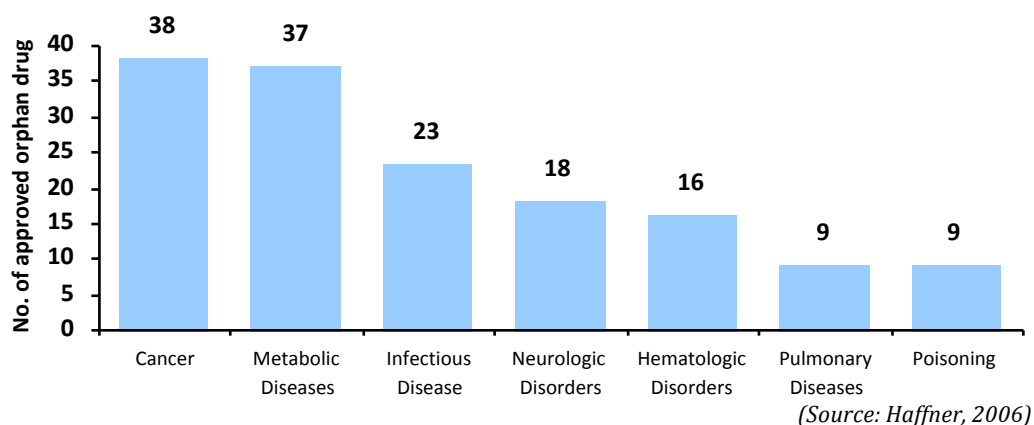


Figure 4 The Top Seven Rare Diseases with Approved Orphan Drug

The most common criticism of the ODA has been the high price of the orphan drug, which usually exceeds the marginal cost of drug development. Some of the blockbuster orphan drugs have earned huge profits from the ODA market protection. The original goal of the legislation was to ensure drug companies make a reasonable profit on orphan products instead of yielding enormous profits. However, the reality is that although the industry has brought treatments to millions of patients in the US, these products are not cheap.

The high price of orphan drugs is attributed to the seven-year market exclusivity, which has been criticized for the lack of the balance between the objective to stimulate innovation in orphan drugs and the public benefit associated with affordable treatments. NORD complains that the ODA is very protective of the companies that are the first to obtain FDA approval. The increasing cost was also attributed to the lack of competition. Some suggestions

are given to modify the ODA to encourage competition because the market forces will result in lower prices.

Other abuses of the ODA that may threaten the future of orphan drug R&D are summarized as follows:

- Using the definition of 'small market' to broaden the scope of the ODA.
- Accelerating FDA approval process and take advantage of ODA benefits.
- Some orphan drugs have a more extensive market, but they still benefit from ODA incentives. These drugs not only treat the rare disease but also target other common diseases.

These abuses of the ODA made the orphan products enjoy a big market under the protection of legislation designed to stimulate the development of drugs with a small market and little commercial value.

Since the objective of the ODA is to advance the development of drugs for patients with rare diseases, it is important to ensure that the ODA does not lead to high health care costs. The system should secure those appropriate incentives as provided for the private sector, and at the same time ensure prudent use of public resources provided for drug development to make it less expensive. The ODA still needs improvement to encourage more efficient orphan drug innovation and bring more benefits to the public (Rohde 2000).

1.4 The Research Question and Objective

Historically, public interventions have played major role in shaping the pharmaceutical innovation: the Food, Drug and Cosmetic Act in 1938 shaped the foundation of drug development by giving authority to FDA to oversee the safety of drugs; Kefauver Harris Amendment in 1962 set the requirements for

drug approval by requiring drug manufacturers to demonstrate scientifically that a medication is not only safe but also effective; Patent and Trademark Amendments (Bayh-Dole Act) in 1980 exerted a significant influence of public research on the drug discovery and development by permitting university, small business, and non-profit institution to pursue the ownership of an invention from federal government-funded research; and Patent Term Restoration Act (Hatch-Waxman Amendments) in 1984 changed the market environment of drug commercialization by enabling generic pharmaceutical manufacturers to develop a copy of the patented innovative drug without duplicating the clinical and non-clinical studies. The above acts encourage drug companies to develop innovative drugs by offering them a period of marketing exclusivity to recoup the R&D costs, and facilitate the rapid availability of lower priced generic version of the innovative drugs after the expiry of patent protection.

Moreover, public intervention has played a critical role in encouraging the innovation of orphan drug. The ODA is the first and most successful legislation focusing on rare disease area. After its success, many countries enacted the orphan drug legislation. Only a handful of drugs treating rare disease were available before 1983, but since the enactment of the ODA, more than 2000 medical therapies have been designated as the orphan drug, and nearly 500 of these therapies have been authorized marketing approval. The orphan drugs used to the treatment of sclerosis, cystic fibrosis and hemophilia are considered as the biggest breakthrough therapies (OIG 2001), as they have significantly improved the healthcare of rare disease patients. The orphan indication has become increasingly attractive to the biopharmaceutical industry, and it accounts for over one-third of FDA new drug applications. No one can deny that the prosperity of orphan drug innovation is inseparable from the ODA enacted in 1983.

However, there are many debates regarding the amount and degree of the ODA incentives. Most criticisms focus on the highly profitable orphan drugs protected by market exclusivity provision. Some scholars proposed to change

the ODA incentives, such as shortening the duration of market exclusivity or setting conditions for companies to enjoy the rights of market protection. A thorough understanding of the system is essential before changing the legislation, but no empirical study has been conducted to explore the dynamics of the orphan drug innovation system and how the incentives stimulate the production of orphan drugs in this complex adaptive system.

Although market exclusivity has been intensively discussed and criticized in terms of monopoly power, studies have not been conducted regarding whether or not the seven-year-period balance the public cost to encourage innovation in orphan drugs with the public benefit derived from the competitive market. It is necessary to evaluate whether the ODA under-protects or over-protects the orphan drug innovation to its jurisdiction. The effects of under-protection mean that orphan drug development is being under-promoted; while over-protection refers to the excessively long duration of monopoly pricing and the waste of public costs. The outcome of this research provides a sound basis for adjusting the market exclusivity terms to strike a balance between giving the monopoly power to the private sector and offering the benefits to the public sector.

Our main research questions are 1) what is the dynamic of the orphan drug innovation system? 2) How do the ODA incentives influence orphan drug innovation? 3) How can the current ODA be improved to encourage more efficient innovation? This research applies the innovative research method of social simulation to answer the above questions quantitatively.

The research objectives are summarized in Table 1.

Table 1 The Research Objectives

Objective 1	<ul style="list-style-type: none">•To establish a theoretical framework for the knowledge-based innovation by combining the theory of the system of innovation and complex adaptive system.
Objective 2	<ul style="list-style-type: none">•To identify the dynamics and evolution of the system of innovation through modeling the organizaional learning process.
Objective 3	<ul style="list-style-type: none">•To build a multi-agent based model of the system of innovation at the sectoral level based upon the analysis and findings about biopharmaceutical innovation in the US.
Objective 4	<ul style="list-style-type: none">•To examine the influence of the ODA through the model of the sectoral system of innovation.

1.5 Summary

The thesis consists of two parts, the first part describes the orphan drug innovation system and introduces the conceptual model of the sectoral system of innovation; the second part translates the conceptual model into the computational model. Experiments are conducted to further analyze this system to answer the research questions. This is organized as follows:

Chapter 1 is a brief introduction into the central topic of the thesis, including the definition of the orphan drug, the orphan drug innovation process, the background of the ODA, and the influence of the ODA on the orphan drug innovation system.

Chapter 2 focuses on developing the conceptual framework for assessing the orphan drug innovation system. After reviewing the literature, several gaps in current research are identified. To address these gaps, the traditional linear

model, non-linear model, and network model need to be updated. In this research, the orphan drug innovation system is modeled as a complex adaptive system. Thus, Chapter 2 starts with a review of literature on knowledge and organizational learning; it is followed by a detailed review of the system of innovation literature. It ends with a review of the model of innovation literature to identify the merits and limitations of various models, as well as to explore the best combination of the theory and orphan drug innovation system. As will be illustrated in the following chapters, this theoretical model incorporates the advantages of knowledge-based view of the company and focuses on the features of complexity and dynamics to enhance the explanatory power of theory of the system of innovation at the sector level.

Chapter 3 is dedicated to the Orphan Drug Act. This chapter concentrates on reviewing the incentives offered by the ODA and the influences exerted by these incentives. It analyses the success of the ODA in bringing a number of treatments to rare disease patients, and identifies the inefficiency caused by the 7-year market exclusivity and other abuses which make the ODA controversial. In the end, this chapter presents some proposed solutions to improve the current legislation.

Chapter 4 brings the theoretical exploration one step further by presenting the conceptual model of orphan drug innovation. More specifically, this chapter introduces the orphan drug innovation process and various roles of players in the system; in addition, the technological and structural changes and their influences on this sector during last decades are discussed. It firstly describes the orphan drug discovery process and its evolution from 1983, followed by explaining the unique orphan drug designation, and then presents how to develop an orphan drug to achieve marketing approval. Finally, the ways of commercializing orphan drugs are discussed.

Chapter 5 presents the methodology adopted in this research. It shows how to translate the conceptual model into the computational model and how to

construct a computational model of orphan drug innovation, including the methodology of social simulation; the explanations about the logic behind modeling, the modeling tools; the ways applied to model the complex adaptive system of innovation; and finally the Genetic Algorithms used to model the innovation activities.

The theoretical model presented in Chapter 2 is highly abstract and simplified. As a result, chapter 6 examines this model and applies it to fit the reality before starting the modeling of orphan drug innovation. In this chapter, the innovation activities are modeled as the process of organizational learning, and the innovation outcomes of the organization by different learning strategies are discussed.

Chapter 7 examines the orphan drug innovation system. It first presents the orphan drug innovation model by extending the model from Chapter 6. The chapter sheds light on our research questions. The performance of the system under different conditions are examined and explained. Moreover, this chapter discusses some controversial issues around the ODA.

Chapter 8 concludes the thesis and summarizes the contributions of this study. Plausible recommendations for improving the US ODA and designing orphan drug legislation in other countries are elaborated here. Possible future work extended from this research is also suggested.

Chapter 2 Knowledge, Learning, and System of Innovation

2.1 Introduction

Knowledge generation and diffusion have been considered the most important factors in the turbulent business environment. Knowledge is the core of innovation studies, and the public policies for science, technology, and innovation have always facilitated knowledge creation and diffusion. Knowledge-intensive industries are believed to be at the core of economic growth; thus, knowledge-intensive sectors have gained much attention in recent years with the aim of identifying factors influencing knowledge creation, diffusion, and application. The methodology in generating knowledge has become the main agenda for companies and policymakers in knowledge-intensive sectors, including the biopharmaceutical industry.

The rapid changes in science and technology drive organizations to develop innovative products, so it is vital for them to generate knowledge efficiently. With intangible assets becoming increasingly critical to a company's competitiveness, organizational learning is the way to prompt innovation. Organizational learning is a trial-and-error, path-dependent, and target-oriented process, through which organizations acquire, refine and create knowledge to generate innovation (Levitt and March 1988, Levinthal and March 1993).

Traditionally, innovation is the discovery of new scientific or technical principles. This contrasts with modern innovation theory, which bases innovation on learning that, not only includes the discovery of new technical and scientific principles (exploration) but also stresses on the recombination and adaption of existing knowledge (exploitation). The exploitation-exploration framework distinguishes two patterns of learning behaviors. The “essence of

exploitation is the refinement and extension of existing competencies, technologies and paradigms”, while the “essence of exploration is experiment with new alternatives” (March 1991). The dynamic process of exploitation and exploration are the key sources of an organization’s competency (Teece, Pisano et al. 1997).

Innovation is an important competitive weapon in the era of globalization. Globalization has increased the complexity of innovation, and the research surrounding it reflects this shift from a linear to more complex manner. For example, in recent years, research has begun to apply a systems approach to study innovation. Based on the system view, the system of innovation (SI) comprises of components and relations. The components refer to organizations and institutions, such as companies, universities and public agencies responsible for making policy, while the connections refer to the interactions among these organizations. The SI approach is focused around knowledge and the learning process, so it specifically emphasizes the creation of new knowledge through innovation. By adopting the viewpoint of knowledge and organizational learning, the SI theory enables us to depict a relatively complete picture of the system of innovation.

This chapter explores the theory of SI and develops the theoretical basis of the thesis. We firstly take up the issue with the SI by introducing knowledge and organizational learning, which are the principal drivers of the SI. Knowledge and learning is the source of a company’s competitive advantage, because this is the basis through which a company can innovate new products and services, or improve existing ones. The second part of the chapter deals with the system of innovation. The boundaries of the SI can be classified as national, regional, or sectoral. All these approaches are complementary rather than exclusive. The third part of the chapter describes the evolution of the different models of innovation, which enable us to understand, assess and optimize the SI. The model of innovation is developed from the early-stage model that considers innovation as a linear process of functional activities. But, it also relies on the

non-linear model that emphasizes on the feedbacks on sub-processes, as well as the network model that includes diverse actors and the actors' interactions. Later, it shifted to the latest system model of innovation—the complex adaptive model that emphasizes on the socio-economic context. The concluding part makes some key observations of studying the innovation of knowledge-intensive sector and presents the framework of the complex adaptive model of innovation in the orphan drug, which is the theoretical foundation for the further computational modeling.

2.2 Knowledge and Learning

“It is assumed that the most fundamental resource in the modern economy is knowledge and, accordingly, that the most important process is learning (Lundvall 2010)”. Organizations have become more knowledge-intensive and reliant on innovative knowledge to create values. The creation of knowledge is unlikely to take place without learning. Knowledge and learning are the two central concepts in studies about innovation.

2.2.1 Knowledge

From the economic perspective, innovation is regarded as an outcome of knowledge production: firstly, innovation represents something new and extends any existing knowledge; secondly, innovation can be viewed as the knowledge that is in demand (Lundvall 2004). Knowledge shapes the pattern of firm's learning behavior and further shapes the innovation outcomes.

There are four different types of knowledge that can be categorized as: know-what, know-why, know-how and know-who (Lundvall and Johnson 1994).

Know-what refers to “the knowledge about facts”. It is similar to what is normally called information.

Know-why refers to the “scientific knowledge of principals and laws of motion in nature, in the human and in society”. This type of knowledge is critical for the innovation.

Know-how refers to the “skills”. Skills are defined as “a capability for a smooth sequence of coordinated behavior that is ordinarily effective relative to its objectives, given the context in which it normally occurs (Nelson and Winter 1982)”.

Know-who refers to “specific and selective social relations” and implies knowledge about what others know and the extent to which their knowledge can be applied to solve someone’s own problem.

The above explanations about different types of knowledge have helped in understanding knowledge creation and learning in the innovation system (Lundvall 2010). Know-what and know-why can be obtained by reading books, attending lectures and gaining access to the dataset, while know-how and know-who can be achieved through practical experience and social interactions. This can be explained in another taxonomy of knowledge.

Knowledge can be classified based on its nature as, explicit knowledge and tacit knowledge (Nonaka and Konno 2005). Explicit knowledge is characterized as declarative knowledge; it can be codified in numbers or words and shared in the form of data. Know-what and know-why are similar to explicit knowledge. Tacit knowledge refers to the knowledge that is neither visible nor expressible; it’s deeply rooted in the individual’s actions and experience, which makes it difficult to communicate and share. Know-how consists of a considerable amount of tacit knowledge and know-who is tacit knowledge, both of which are embedded in the social practices and very difficult to codify and transfer.

2.2.2 Knowledge in Organizations

Firms can directly attain competitive advantage from innovation. The innovation ability of any firm depends on its knowledge and its ability to utilize it. The knowledge-based view (KBV) emphasizes on the role of knowledge on firm's innovation performance. KBV has improved the understanding of the process in which knowledge inputs are converted to products or services and the role of firms in this process (Choo and Bontis 2002).

The KBV has attracted much attention in recent years in innovation analysis. It identifies factors that impact knowledge creation, diffusion, and application. It also conceptualizes firms as organizations for developing and transferring knowledge, since firms develop their knowledge by learning within and subsequently transferring their knowledge in exchange for creating value (Macher and Boerner 2012).

2.2.3 Organizational Learning

Innovation and learning are the two facets of R&D because firms invest in R&D to pursue innovation and develop their ability to learn.

Learning can occur at different social levels. It can be differentiated between individual process and collective processes. At the micro level, although learning occurs as an individual process, it does not take place only at the individual level. Learning is also an interactive process between people and organizations. It involves intense and complex interactions within and between organizations. Individual learning means the acquisition of knowledge, understanding, skills, and competencies by individuals through the form of education and training. It is naturally critical for the growth of companies' innovation ability. But, organizations have to move beyond individual learning and stimulate organizational learning to create innovation sustainably.

2.2.3.1 Intra-organizational Learning

Intra-organizational learning refers knowledge created and developed within the boundaries of the organization. In contrast to new knowledge, the existing knowledge or knowledge base is the sum of the knowledge an organization has achieved. Organizations can learn by improving existing knowledge, which, integrated with the knowledge base, leads to new products or processes. It is evident that the knowledge base is developing while the organization learns; learning makes the knowledge base larger and more versatile. Different patterns of organizational learning have different effects on the knowledge that an organization can gain.

Exploitation and exploration are the twin concepts underpinning organizational learning (Table 2). Both exploitation and exploration work together to drive the process of knowledge creation. Exploitation refers to “learning based on local search, experiential refinement and selection, and reuse of existing routines; exploration refers to learning based on the process of concerted variation, planned experimentation and play (Baum, Li et al. 2000)”. The outcome of exploitation is predictable, while the outcome of exploration is much more uncertain (Powell, Koput et al. 1996). If the organization only engages in the exploration, it will possibly suffer from never gaining any useful knowledge, and the organization that engages exclusively in the exploitation will be trapped in the situation of “suboptimal equilibrium” (Levinthal and March 1993).

Table 2 The Difference between Exploration and Exploitation

	Exploration	Exploitation
Process	Discontinuity	Step by step
Learning	Radical learning	Incremental learning
Product	Revolutionary and fundamental changes, novelty	Minor improvement or simple changes, not sufficient novelty
Uncertainty	High	Low

Although organizations can engage solely in either exploration or exploitation, most firms operate through both types of learning to benefit from the dynamic

learning opportunities. Such organizations are termed as ambidextrous organizations. Both patterns of learning require very different strategies, structures, processes and cultures (O Reilly and Tushman 2004).

The methodology behind dividing resources between exploration and exploitation affects the performance of the organization. The uncertain and unclear feedback links exploration to its slower and less precise outcomes than is the case with exploitation. For instance, basic research is generally a very long journey with less certain outcomes, because it compromises the certainty of success for the novelty of the knowledge, longer time horizons and more diverse influences that surpass existing ones. In the field of rapid science and technology development, organizations have to adapt considerably, and can change their behavior incrementally by exploitation or radically through exploration. In most cases, organizations exhibit a mixture of both learning regimes; thus, it is important for the company to choose an appropriate learning strategy and reach an appropriate equilibrium between the exploitation and exploration; otherwise, it may end up suffering from sub-optimization.

However, as the outcome of exploitation and exploration are well addressed, the studies that take longitudinal and dynamic perspectives of the topics are scarce. There is a gap in the organizational learning studies examining the process rather than the outcome of exploitation and exploration, especially the relationship between the learning behavior and the outcome.

2.2.3.2 Inter-organizational Learning

Inter-organizational learning refers to the transfer of knowledge from outside through collaboration and acquisition. By establishing networks with other organizations, firms can gain the knowledge they lack. Specifically, in knowledge-intensive industries where inter-organizational learning is more important, when knowledge is broadly distributed, the locus of the innovation is

found not only in the organization but also in the connection of inter-organizational relations (Powell, Koput et al. 1996).

The organization is able to achieve better performance by engaging in exploration and exploitation at the broader level of the social system rather than individual organizations (Gupta, Smith et al. 2006). Some organizations may specialize in exploration while others may excel at exploitation, so collaboration will yield a better outcome. The inter-organizational exploration implies that the organizations in an alliance transfer and absorb the partners' knowledge base, while inter-organizational exploitation refers to organizations accessing their partners' knowledge base for complementarities and maintaining its distinctive base of specialized knowledge (Grant and Baden-Fuller 2004).

The ambidextrous alliance is defined as the inter-organizational learning that involves both exploration and exploitation. The ambidextrous learning strategy enables organizations to not only simultaneously exploit existing knowledge but also explore new opportunities from outside. Organizations are not capable of acquiring, integrating and creating knowledge to the same extent, so they are not equally efficient learners. Because of differences in their learning capability, organizations, in turn, show different learning performances.

The research about how the organization learns adaptively through the network and how the organization evolves with its partner is scarce. This research will address this gap, and reveal the dynamics of inter-organizational learning, with emphasis on the relationships between exploration and exploitation.

2.3 System of Innovation

From 2.2, we can find that firms generally are not able to innovate in isolation, but in the collaboration with partners. The partners include firms (suppliers, customers, competitors, etc.), or non-firm organizations such as universities, government, and other intermediaries. One of the main features of the system-oriented approach to studying innovation is the emphasis on the interdependency and interactive learning (Edquist 2001). Various organizations and the interactions among them make the system approach very useful in understanding and analyzing the innovation. In the system approach of innovation, the interdependencies and interactions between the actors in the system are described as the most important characteristics (Edquist and Johnson 1997).

2.3.1 What is the System of Innovation?

The system of innovation (SI) stresses on the complex interdependent interactions among various elements in the innovation process. The system approach has extended the previous innovation model in conceptualizing innovation as an interactive, dynamic process featuring learning processes and involving external organizations.

The concept of the SI was firstly introduced by Lundvall in 1985. In the theory of the SI, innovation and learning process is at the center of focus, which is based on the understanding that innovation is a process of creating new knowledge (exploration) or combining existing knowledge (exploitation) in new ways.

The System of innovation is entirely different from each other, for instance, the variations in the production, knowledge, institution, relationships and network structure. The SI can be classified by geographical scale, technology, and industrial sector. According to these factors, the concept of the 'system of innovation' is now widely accepted to be analyzed on the national, regional and

sectoral level. The main emphasis was initially on the national innovation system (Freeman 1987, Lundvall 1992, Nelson 1993), and then it inspired the research on the regional and sectoral level (Malerba 2004).

The NSI, RSI and SSI are complementary to each other rather than exclusive to each other. As shown in Figure 5, there are two NSIs (NSI-1 refers to NSI of country 1 and NSI-2 refers to NSI of country 2), three RSIs (RSI-a refers to RSI of the region a, RSI-b refers to RSI of the region b and RSI-c refers to RSI of the region c), and one SSI. From Figure 5, we can see the regional systems of innovation are embedded in national systems of innovation; moreover, it's not difficult to find how the SSI relates to the two geographical systems of innovation, the SSI overlaps with the RSI-b and parts of the NSI-1 and the NSI-2.

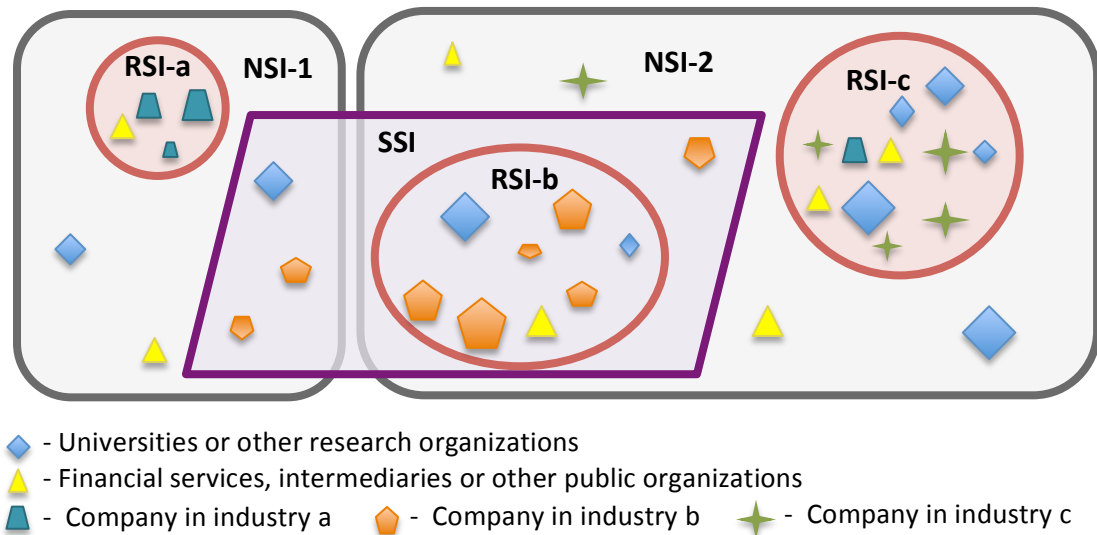


Figure 5 The Illustration of NSI, RSI, and SSI

2.3.2 The National System of Innovation

The notion of the National System of Innovation (NSI) was introduced by Freeman (1987), and is mainly associated with two other authors: Lundvall (1992) and Nelson (1993).

The NSI is a “set of distinct institutions, which jointly and individually contribute to the development and diffusion of new technologies and provide the framework within which governments form and implement policies to influence the innovation process. As such, it is a system of interconnected institutions that create, store and transfer knowledge, skills, and artefacts which define new technologies (Metcalf 1995)”. The NSI comprises the economic, social, political, and organizational factors that influence the development, diffusion, and use of innovation (Edquist and Johnson 1997). The actors of the NSI are from both private and public sectors, so their behaviors and interactions play an important role in the innovation process at the national level. The institutions, on the other hand, support the NSI by providing capital (financial service), skilled labor (education service), infrastructure (public service), policy and regulation (government service) and other supportive mechanisms.

The research on NSI is the most popular compared with the RSI and SSI for two reasons: the first reason is the big difference between the various national systems, such as institutional set-ups, investment in R&D, actors and performance; the second reason is that the public policy influencing innovation are almost on the national level.

2.3.3 The Regional System of Innovation

Since the introduction of the NSI concept, there have been considerable debates about whether the ‘nation’ is an appropriate level for the analysis of innovation. The NSI approach stresses on the homogeneity within a country, but the fact is that the innovation can vary significantly in terms of actors, relationships and the role of public policy (Korres 2013). There is growing empirical evidence that, in many cases, the learning process is highly localized. Consequently, researchers have developed a regionally based approach of the innovation system, and the ‘region’ usually refers to a geographical area within a country. The concept of RSI has gained much attention from researchers and policymakers since the early 1990s. It has become a promising analytical

framework for improving our understanding of the innovation process at the regional level.

The main features of the RSI are: “agglomeration economies, institutional learning, associative governance, proximity capital, and interactive innovation (Cooke 2002)”. The firms are considered as the main factors in RSI but within a regional boundary. They are from the same industry or from the closely related industries that are in close geographical proximity. As a critical element in the innovation process, learning has specific and local characteristics and can be improved through tailored institutional changes and oriented policies. The government can exert influence to improve the innovation capability of the RSI by developing policies that support the local learning processes.

From 2.3.1 and 2.3.2, we can find that both the NSI and the RSI are defined by spatial boundaries. Besides the geographical dimension, another approach has been applied to describe SI based on sectoral characteristics. The Sectoral Innovation System (SSI) is defined as a system of organizations that develop a sector’s products and create a sector’s knowledge.

2.3.4 The Sectoral System of Innovation

2.3.4.1 The Concept of the SSI

It is evident that there is a difference among various technological systems, such as R&D process, product regulation, government policy, and market characteristics. These technology-specific differences have significantly influenced the innovativeness of different sectors. Therefore, some scholars suggest that the technical system can be analyzed at the sector level. The pattern of innovation in different industries are varied, in terms of the characters of innovation, learning and socioeconomic environment.

2.3.4.2 The Key Factors in SSI

Sectors are characterized by “specific knowledge bases, technologies, production processes, complementarities, demand and population of heterogeneous firms, non-firm organizations and institutions ”(Malerba 2002). Different from the SI approach described in the previous sections, the SSI is defined based on related or substitutable product groups that serve a certain demand and have a similar knowledge base. The SSI is based on three building blocks: knowledge and technologies; actors and networks; and institutions (Malerba 2005).

Knowledge and Technologies

Knowledge plays a critical role in innovation, which has been strongly emphasized by evolutionary literature and knowledge-based economics. In the evolutionary literature, the knowledge base and the learning process differ greatly among sectors.

Actors and Networks

The actors and networks in a sector are heterogeneous, and connected through market or non-market relationships. The organizations are featured by specific organizational structures and learning processes. They interact through the process of innovation.

In the SSI, firms are at the center as they are involved in the innovation, production, and distribution of sectoral products, and in the creation, adoption, and diffusion of new knowledge. The firms are featured by productive technological and market specialization, and they have different competencies, structures in the process of learning and knowledge accumulation. Other types of actors in the SSI are non-firm organizations including universities, financial services, government and local agencies. They support the SI in various ways, and the types and functions of non-firm organizations vary among sectors.

In the SSI, heterogeneous agents are connected in different ways through market and non-market relations (Malerba 2002). The networks are different because of the different characteristics of the knowledge base, learning process, actors, relations, and dynamics. Moreover, the intensity of the links among actors differs across sectors, and the relationship between firms and non-firm organizations is the key source of innovation in high-tech sectors.

Demand

As discussed above, SSI is composed of heterogeneous actors characterized by knowledge and learning process, so their demands are heterogeneous. In the SSI, the demand of system is not the simple sum of each actor's demands, but a set of interacting actors under the influence of institutions. The demand is a stimulus for innovation as well as a constraint. Coupled with knowledge and technology, demands determine the nature of the problems that firms aim to solve in their innovation and production, and determine the incentives and constraints on particular behaviors and organizations (Malerba and Mani 2009).

Institutions

The institutional infrastructure directly or indirectly shapes the activities and interactions of actors in the system. The performance of the sector is influenced by norms, routines, habits, laws and policies. It is evident that the institutional differences exist not only between countries and regions but also within sectors.

Besides institutional differences, the national institutions among sectors are different and thus have different influence. In some countries, the features of national institutions favor some sectors better than in other countries. Therefore, some specific sectoral systems are thriving in a country because the institutions of that country provide a more suitable environment for these sectors; and in other cases, the national institutions may limit or even impede the development of sectoral innovations (Malerba 2002).

According to the SSI concept, the successful innovations emerge from a favorable combination of all the above factors. Hence, in order to understand the dynamics of a given sector, researchers have to consider these three factors and the interactions among them.

2.3.4.3 The Advantages of the SSI

The SSI has shown its advantages in many respects. Firstly, from the above, it is obvious that sectors differ in their technologies. Knowledge, as a critical factor of the innovation system, is also sector-specific. The SSI is very helpful in getting a comprehensive understanding of the system of innovation within a particular knowledge base. The SSI is also good at studying the performance of a specific sector at the global or country level. Secondly, although public interventions are designed and implemented at the national level, the policies targeting different sectors show many distinctions. In many countries, policies for innovation vary between sectors. Compared with the NSI and RSI, the SSI pays a lot of attention to the knowledge base, learning process and the heterogeneity of actors, non-firm organizations and institutions. Moreover, it emphasizes the evolution of the system. Thirdly, the approach of the SSI delimited to specific technological fields or products is a good way to understand the dynamics of an industry and identify the factors influencing the performance of the system and finally contribute to developing public policy indications. It has been applied in many industries, including the pharmaceutical industry (McKelvey and Orsenigo 2001), semiconductor industry (Kim and Lee 2008), capital goods industry (Kim and Lee 2008), automobile industry (Xi, Lei et al. 2009), energy industry (Rogge and Hoffmann 2010) and vegetable breeding industry (Liu, Jongsma et al. 2015).

However, SSI has not been addressed too much. It is a relatively new theory, and certainly has some limitations. The SSI has been criticized on different levels. For example, the system boundary based on existing products did not account for new products (Schrempf, Kaplan et al. 2013). The current study is mainly

about the analysis of the upstream part of the system, like R&D, and the scope of the analysis should be extended to the production, sale and distribution part.

2.3.5 NSI, RSI, and SSI

In summary, since this research focuses on the innovation of orphan drugs, the concept of SSI is a relevant and appealing framework. The sectoral system of innovation features a well-articulated, multi-dimensional, integrated, dynamic and systematic view of innovation, which shows its advantage not only in understanding and analyzing a sector but also in allowing comparative analysis across a range of industries.

As shown in Table 3, while the NSI and RSI fail to include sectoral factors in its conceptual framework, the SSI concept enables the analysis of actors and innovation performance at the sectoral level. However, many SSIs do not show national differences in its framework; it does not explain how and why many pioneering companies within a particular industry usually come from certain countries. The innovation activities and performances primarily rely on sector-specific characteristics, and it is also influenced by the national and regional conditions. This is why the same sectors have distinct patterns of innovation in different areas.

Table 3 The Summary of NSI, RSI, and SSI

	Knowledge Variety	Geological Space	Main Actors	Institution
NSI	A wide variety	Nation	Industry, government and research organization	National policies, laws and national finance supports
RSI	Major in several loosely or closely related areas	Region	Universities, industrial enterprises, public research organizations	Local policies and regulations, trust and reliability among actors
SSI	Specific in one area or closely related areas	Globalization, nation, or Region	Firms, research organizations and financial institutions	Standards and regulations

The definition of the SSI is flexible to allow researchers to focus on what they think is critical to system innovation. It has been pointed out how the SSI and NSI exist interdependently, and how sectors usually tend to cluster from the viewpoint of RSI. The 'system' could be applied and defined loosely based on the research aim and object. It is evident that as the industry becomes more globalized, the SSI is more likely to be analyzed at the global level. The research on the sectoral patterns of innovation activities has shown that there is a big difference between sectors, and even within the same sector, the innovation activities differ between countries. The sectoral patterns of innovation are determined by the technological regimes, knowledge base, learning process, public organizations and related regulations, all of which are somewhat different across countries; and the national systems of innovation have a big influence on the sectoral pattern of innovation (Malerba 2002).

For studying the orphan drug innovation in the US, it is proposed to consider the SSI-NSI interface with a particular emphasis on the SSI components. As the legislation of the orphan drug and the institutions of the orphan drug innovation are different among countries, which will be elaborated in Chapters 3 and 4, this research explores the innovation system at the industry level with the consideration of national differences. Studying the interface of SSI and NSI appears attractive as a method of investigating the emergence of new start-ups stimulated by national public interventions at the sector level. By considering the empirical findings of the SSI at the national level, we could also explore how the particular combination of knowledge and technology, actors, networks, and institutions influence the evolution and dynamics of the orphan drug innovation in the US. Therefore, as the purpose of this research lies in generating insights into the dynamics and policies that determine the performance of orphan drug sector, the analysis should apply the SSI approach.

2.4 The Model of Innovation

'Model' as a research framework has been widely used in the study of innovation. It is an important notion in explaining how innovation is generated and what factors affect the outcome of the innovation process. The model is a representation of complex reality, but it cannot take all the factors into account and show all the attributes of the reality. By involving the important or the interesting factors in the model, it is a powerful research tool for us to study the innovation and help us managing innovation effectively.

Understanding the process of innovation has evolved throughout recent decades from the simple linear model to the complex models embodying diverse feedbacks, multiple players and changing social-economic environments. Four generations of the innovation model are summarized in Table 4. The models do not substitute each other; even the first generation of the model has still been used so far.

Table 4 Generations of Innovation Models

	Model	Feature	Strengths	Weaknesses
1 st	Linear Model	Simple linear sequential process	Clear image of innovation process	Lack of feedbacks; No network interactions;
2 nd	Non-Linear Model (Chain-linked Model; Coupling Model)	Multiple interactions among different phases; Emphasis on integrating R&D and market	Feedbacks between phases; Knowledge is created throughout the whole process	No network interactions; no environment factor
3 rd	Network Model (Innovation network)	Multi-players incorporation and external linkages, emphasis on the university	Networking to create innovation; knowledge diffusion	Ignorance of the adaption of actors in the network.
4 th	System Model	Integrating all the factors and their interactions in the model; the adaptiveness of organization	Actors are intelligent and self-organized, emerging features	Complexities

2.4.1 The Linear Model of Innovation

The first conceptual framework for understanding innovation is considered to be the linear model (Godin 2006). The concept of the linear model is from the natural science field. "In the linear system, the relationship between cause and effect is smooth and proportionate. Linear system responds to big changes in a big and proportionate manner and linear systems respond to small changes in an equally small and proportionate way (Kiel, 1995)". One example of the linear model is the mechanic model, which consists of several parts that are interconnected to maintain the operation of the system. In the mechanic system, we can easily know and expect what each part will act in response to a certain stimulus, moreover, it is possible to investigate and predict what the system will perform under various conditions (Plesk and Wilson 2001). The best way to improve the performance of a mechanical system is to decompose the whole system into component elements and then recompose it by integrating the designed solution for each element into an overall system (Rouse 2008).

The linear model of innovation is a set of constructs developed over time (Godin 2006). It has been widely known since the World War II (Kline and Rosenberg 1986), which suggests that innovation happens in a linear fashion from basic research, development, production to diffusion (Figure 6). These activities are visualized as a smooth, one-directional flow from start to end (Edquist and Hommen 1999).

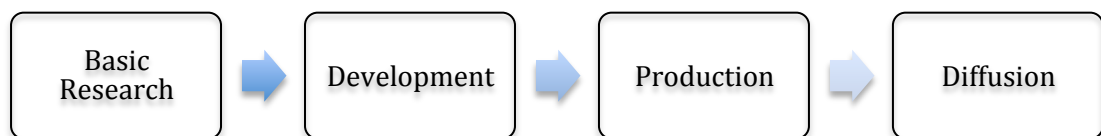


Figure 6 The Linear Model of Innovation

Two versions of the linear model of innovation are developed: 'technology push' model and 'market pull' model (Rothwell 1994). The 'technology push' model is

based on new technology that emerged in the 1950s to 1960s, such as semiconductors, pharmaceuticals, and new materials. These industries focused on the R&D to commercialize the technological changes and satisfy the unmet demand of customers. The innovation process of the 'technology push' model starts from scientific discovery, through technological development, and ends in the market. From mid-1960s to early 1970s, new products were introduced based on existing technology, and the supply and demand were somewhat balanced. As the competition became more intense, companies shift from developing new products with new technology to developing new products by emphasizing on the demand-side factors. The 'market pull' model begins with the market needs that direct R&D and then follows by the manufacture and sale.

Despite its widespread use, the linear model of innovation has faced numerous criticisms. One of the defects of the linear model of innovation is the absence of feedback that is the inherent and essential part of innovation (Kline and Rosenberg 1986). According to that, on one hand, the innovation process is not smooth rather than highly uncertain without adequate information at the beginning. The shortcomings and failures are part of the learning process, and in a learning process that is both radical and incremental, the rapid and accurate feedbacks with appropriate follow-on actions lead to effective innovations. On the other hand, not all the innovation process flows from basic science to applied science and then to the product. Sometimes, the design is essential in triggering technical innovation and redesigning. The problems generated in the process of designing or testing new products may contribute to the basic research, so the direction of causation is reversed in many cases.

Another problem is that the linear model ignores the impact of the collaboration. The university and company are actors in the linear innovation model, but there are a variety of organizations contributing to the generation of innovation. Innovation is characterized as a fundamentally social process in nature (Lundvall 2010), which means that innovation is a collective process involving a variety of actors with different skills and competencies. Therefore, the

cooperation among organizations is important for the successful innovation. A firm's capability to innovate is further shaped by the government intervention, which is also neglected by the linear model. The linear model also implies that if you increase the input on the basic research, you will get more innovation output. But, it is obvious that innovation is a highly uncertain process, and small changes in the initial condition can result in disproportionately large effects.

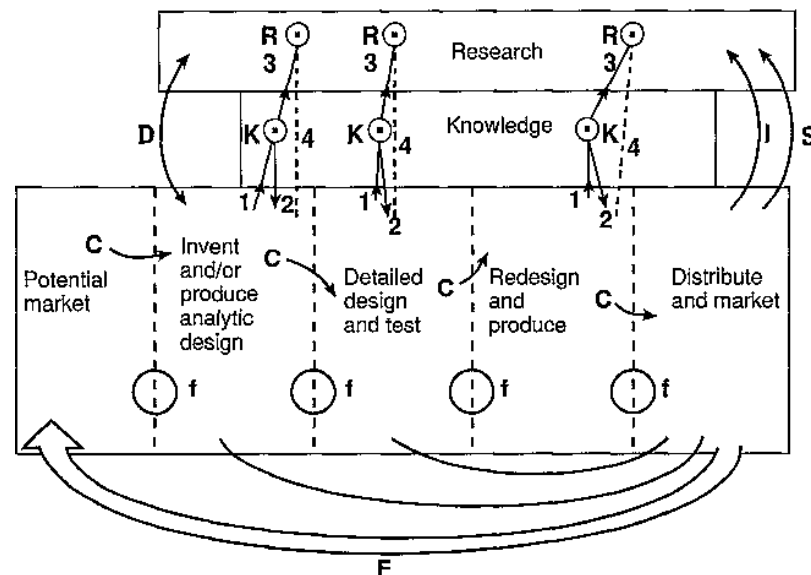
2.4.2 Non-linear Model of Innovation

Since the linear model had been challenged in many aspects, a more complex model was needed for the better understanding of innovation. Scholars realized that 'innovation is neither smooth nor linear, nor often well behaved (Kline and Rosenberg 1986)'.

By definition, non-linearity means 'not in a straight line' or 'the output is not directly proportional to the input'. In the non-linear model of innovation, the activity does not happen sequentially from beginning to the end and the process of innovation is uncertain. Different from the linear mechanic system, innovation management cannot be implemented by hierarchical decomposition, which cannot be used to address the innovation model as it may result in the loss of information about the interactions of elements. In the non-linear model of innovation, the activities are connected by the different types of loops and the innovation cannot be analyzed step by step.

The chain-linked model was first reported by Kline in 1985 (Kline 1985). It was introduced with an emphasis on the complex structure and diverse patterns of innovation. The chain-linked model differs from the linear model in the following ways: firstly, according to Kline and Rosenberg (1986), in the chain-linked model innovation is market-driven, the central process starts with market need, which drives research and design, production, marketing, and distribution; secondly, there are numerous of feedback links in the model and the feedback is the essential part of innovation.

In Figure 7, the feedback paths (C) link each downstream steps in the central chain, and feedback loops (f) connect back from market to upstream research and design; thirdly, the knowledge is not solely generated at the beginning of the process but rather in the whole process of innovation, the accumulated knowledge can be drawn upon along the central chain of innovation (K), when the accumulated knowledge fails to solve the problem a need arise for research to create new knowledge (R). Finally, the research sometimes leads to radical innovation (D) that is rare but marks major changes in its area, in addition, the innovation products contribute to the science (I, S) through the application of new instruments, tools, procedures of technology and information underlying product.



(Source: Kline and Rosenberg, 1986)

Figure 7 The Chain-linked Model of Innovation

In the model, we can understand innovation in two variables uncertainty and product lifecycle(Kline and Rosenberg 1986). Innovation implies uncertainty, and the degree of uncertainty is associated with the amount of improvement in the innovation. In the early stage of product life cycle, the innovation is more related to big changes in the product design, once the accumulated knowledge is inadequate to fulfill the needs new science is created and marked as radical

innovation; in the later stage, the innovation is more concerned with process changes, this kind of knowledge is not considered as science but it's critical to a successful product innovation.

Similar to the chain-linked model, the coupling model featured by the coupling between technology and market is another attempt to add uncertainty to the linear model with complex structure and multiple feedbacks (Rothwell 1994). But the same as the linear model, as a firm-level model, the inter-organizational learning and the change of environment are ignored. The non-linear models extend the linear model because it draws a complete picture of the innovation process and helps us get a better understanding of the innovation. However, it 's only a conceptual model than a useful analytical framework (Godin 2006).

2.4.3 The Network Model of Innovation

The technological change can influence the social structure, and the social structure places its impact on an organization's ability to produce knowledge. From 2.3.3, we found the external sources of the knowledge are important to the innovation. The ability to explore and exploit external knowledge is obviously a critical component of the innovation capability. Hence, the research of innovation has moved from an intra-organizational level to inter-organizational level.

The term 'network' is an abstract concept referring to a set of nodes and ties linking each other. Network is derived from natural science, for example the neural network, but it has been widely used in the social science including organization theory, operational research, healthcare and linguistics. The network approach marks a shift from research that centers on individual firm towards a more systemic way of addressing social phenomenon (Burt 2002). The high-tech industry, such as biotechnology and electronics, has been the favorite area for studying network effects.

The typical innovation network includes nodes representing individual organizations, and ties representing the collaborative relationship between two organizations. Figure 8 is an illustration of a network of innovation in the biopharmaceutical industry, the node A represents a biopharmaceutical company, B represents a university, and C represents a biotechnology company. The ties among them mean they have collaborative relationships. The benefits of the network include getting access to the new market and knowledge; speeding products to market; and sharing risks. The network not only plays an important role in creating innovation, but also facilitates the diffusion of innovation. Following the distinction between exploration and exploitation, the innovation network has been analyzed for their ability to exploit existing areas (Krackhardt 1992) and explore new areas (Duysters and Man 2003).

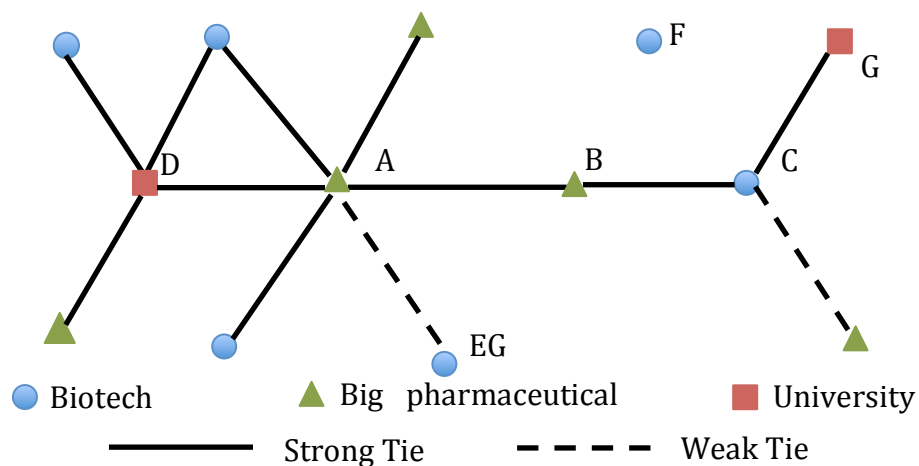


Figure 8 The Illustration of the Network of Innovation

Direct Tie and Indirect Tie

Several key concepts have been applied to analyze different types of networks and assess their performances. The network position and the absorptive capacity have a significant influence on the organization's innovation (Tsai 2001). Firstly, considering the difference between direct ties and indirect ties, A can reach B by the direct tie AB and A can further reach G by the indirect tie BC and CG. The number of the direct ties an organization maintaining has a positive

influence on the innovation output by facilitating knowledge sharing, bringing complementary resources, and enlarging the project scale (Ahuja 2000). The greater the number of the collaborative relationships formed by a start-up, the more patents it could achieve (Shan, Walker et al. 1994). Building a large number of indirect ties may be a more effective way for actors in terms of taking the advantage of the network size without paying the cost of network maintenance than engaging in direct ties (Burt 2009). The second notable contrast is the distinction between strong ties (for example, the tie between A and B) and weak ties (for example, the tie between A and E). A strong tie means the interactions between organizations are on a regular basis, while a weak tie is an acquaintance (Granovetter 1973). The strong ties built on common interests and information reinforce existing views, but the weak ties generate novelty by introducing new information (Gretzinger, Hinz et al. 2011).

The Density of Network

The density of a network is the degree of the dyadic connection among nodes, and it's measured by the percentage of the number of existing ties divided by the number of all possible ties. Dense network improves the knowledge transfer through efficient commutation and trustful cooperation. Closed network means everyone is connected to each other. It creates an advantage for the firm by getting access to the external knowledge and lowering the risk of cooperation. However, frequent long-term interactions between a limited number of firms can result in generating increasingly conformable and homogeneous knowledge and thereby less innovative product (March 1991). Dense networks are associated with substandard performance (Burt 2000). By contrast, a more dispersed structure has greater potential for generating novelty product through getting access to a wide and diverse range of knowledge (Ahuja 2000).

Centrality

Different locations in a network result in the different ability of the organization benefitting from alliances. The study of biotechnology start-ups indicates that firms' number of collaborative relations is positively related to its innovation

output (Shan, Walker et al. 1994). The degree of centrality is a measure of the direct connectedness of a firm with other firms in the network (for example, the degree of A is 6 and the degree of F is 0). Its high value indicates that the company is highly connected, so firms can control and brokerage knowledge in the network (Knoke and Yang 2008). In the research of the formation of inter-firm learning networks for biotechnology start-ups, the centrality is related to the fast growth of small companies (Powell, Koput et al. 1996). Firms with the central location have more timely access to the new knowledge. Moreover, the central position in the network has a reciprocal influence on R&D collaboration: the large number of R&D ties make an organization central connected, while central connectedness intensifies an organization's capability to explore through the network.

The Diversity of Partners

Innovation occurs more effectively when there is knowledge exchange between fields, for instance, between different technological areas, sectors, and regions. The studies have demonstrated that the innovation is influenced by the partners that the company collaborates with. Innovation, particularly complex and radical innovation, benefit from networking with a diverse range of partners that facilitate the sharing of the different knowledge base, learning patterns and management skills. In Figure 8, we can see that A's partners are more diverse than B', which makes A get access to the leading basic research achievement due to the relationship between universities. The incremental innovation relies on partnering with customers, while radical innovation demands more interaction with suppliers (Pittaway, Robertson et al. 2004). Both incremental and radical innovations are important for companies to achieve successful innovation. Another study shows that organizations with better global positions can more easily reach varied resources in pursuit of novelty, and these opportunities can overcome the limitation of local homogeneity or lock-in (Whittington, Owen-Smith et al. 2009).

Structural Hole

Another important dimension of a firm's network is the degree of the connectivity between a firm's partners. A structural hole, by definition, is a relationship of non-redundancy between two nodes (Burt 2009). In Figure 8, the gap between A and C is a structure hole with B bridging the hole and providing the network benefits that are in some degree additive rather than overlapping. The structural hole creates a competitive advantage for the firm whose network spans the hole which brings the advantage by increasing the value of cooperation; moreover, the firm in the structural hole is able to broker the flow of knowledge between two sides and control the projects that bring together the firm from the opposite side (Burt 2002). The organizations on either side of a structural hole transfer the information in different flows, and the structural hole enables the organization to reach more organizations indirectly with less redundant information. The evidence shows that there is a brokerage advantage in producing ideals (Burt 2004). The organization bridging the structural hole has an edge in information about both sides; therefore the organization brokers the connection between two sides and enjoys the economic benefits of controlling the collaboration. The brokerage is more valuable for the network in which organizations are closely interconnected (Burt 2009). According to the research, in a network where relations are of a short period or not on a mutuality base, the advantage of structure hole is obvious (Walker, Kogut et al. 1997).

Social Capital

"Social capital is the sum of the resources, actual or virtual, that accrue to an individual or a group by virtue of possessing a durable network of more or less institutionalized relationships of mutual acquaintance and recognition (Bourdieu and Wacquant 1992)". The source of social capital is derived from the structure and content of the actors' relations (Adler and Kwon 2002). The actors' social capitals are influenced by the networks they are embedded in. In a fully connected network, firms have access to social capital that helps the norm development and information diffusion, while firms in an open network have no social capital to rely on (Walker, Kogut et al. 1997).

The brokerage across the structural hole is social capital, the networks that span structural hole are correlated with learning, creativity, adaptive implementation, and more positive evaluations (Burt 2002). But, a study provides an example of the distinctions between social capital and structural hole. In the early stage of network formation, structural holes are more valuable, but as the network becomes more well-established, the startups prefer to increase social capital rather than exploiting structural holes, because the network is densely connected after a long time, and the relationships are complementary and mutual dependent (Walker, Kogut et al. 1997).

From the review, we can see a number of the research on innovation network has focused on examining the impact of the actors' position and ties in the network or the network's structure. Before 2000, few studies had applied longitudinal data to analyze network and little attention had been paid to the evolution of the entire network. A study about the biotechnology industry accounts for the dynamics of innovation network during the period from 1988 to 1999, and its results indicated that the network had become more cohesive and diverse (Powell, White et al. 2005). It also indicated that the early dominator-large multinationals and first-generation biotech firms had collaborated to commercialize the lead products.

In recent years, with the development of our understanding of the SI and the increasing complexity of the SI, researchers start to study the SI with the large-scale network by the model of the complex adaptive system that stresses on the dynamic and evolutionary feature of the network. The research addresses that the network dynamics are generated from a field where social, economic, political and scientific factors shape the patterns of actors' behavior. Therefore, the innovation process in the model is non-linear and dynamic; the actors are intelligent and interdependent, the environment is changing and influential.

2.4.4 The Complex Adaptive System Model of Innovation

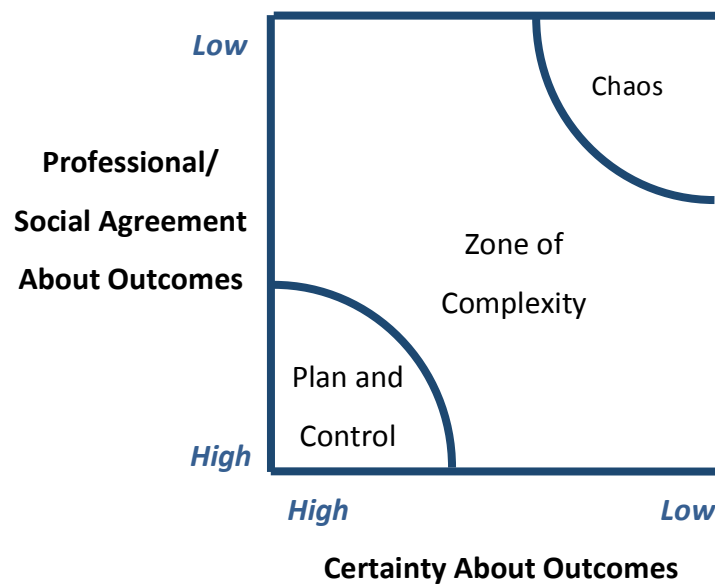
By reviewing the linear and chain-linked models of innovation, it is not difficult to find that innovation should be viewed as changes in a complete system, which includes knowledge, facilities and products, social and political environment. Compared with the network model of innovation, which focuses on the 'network', the system model of innovation stresses on the 'actor' and the 'network'. As discussed in 2.3, the innovation network approach studies knowledge generation and diffusion based on network structure. In contrast, the innovation system approach primarily concerns organizations (Nelson 1993). Because the system of innovation is a social system, it is conceptualized in terms of organizations and their interaction (Lundvall 2010).

The social dimension of the innovation had been ignored for a long period of time, because the technical change was considered as a socially exogenous phenomenon (Schienstock and Hämäläinen 2001). However, innovation is a socially embedded process, and it emerges among social organizations. The process of learning involves a variety of social actors from different parts of the economic structure. The narrow definition of the actors in the system of innovation includes firms, universities, research intuitions, and government technology agents. The wide definition of the innovation system includes the organizations facilitating the learning process and providing additional input into the innovation process. Examples of supporting organizations include training organization, banks, venture capitalists, and government agents. Altogether, the innovation system includes "all important economic, social, political, organizational, institutional and other factors that influence the development, diffusion and use of innovations (Edquist 2005)".

In an effort to further develop the complex adaptive model of innovation, it is useful to relate it explicitly to the complex adaptive system theory, which has been applied much more in the field of natural science than in the field of social science.

2.4.4.1 What is the Complexity?

As shown in Figure 9, linear systems have a very high level of certainty (the outcomes from actions) and agreement (among the agents involved in the actions), so they are easily controlled and planned. For chaos systems, there have very little certainty and agreements, so they produce very intricate and unpredictable dynamics. The complex system is a state between order and chaos, so the rich dynamic behavior is generated from the simple interactions among a large number of elements.



(Source: Stacey, 1996)

Figure 9 Stacey Diagram: The Zone of Complexity

2.4.4.2 Complex Adaptive System

Complex behaviors that arise as a result of non-linear interactions between different components of the system at different levels are a feature of both natural systems such as the brain or the immune system as well as artificial systems such as artificial neural networks and other evolutionary programs. These systems have come to be known as Complex Adaptive Systems (CAS).

CAS arose from studies about complex theories. The 'complex' indicates that the diversity refers to a wide variety of elements; 'adaptive' implies the ability to

learn from experience and improve its capability; and 'system' is the collection of the interacting elements (Begun, Zimmerman et al. 2003). Over the past decades, CAS has been the focus of studies across a variety of areas, including the human immune system, the Internet, electric power grids, the stock market, social groups, and human society.

The elements in CAS exhibit a set of basic characteristics:

Independent Agents The system is composed of independent agents that interact and adapt to learn (Holland 2006). Their behavior is based on "physical, psychological, or social rules rather than the demands of system dynamics (Rouse 2000) ".

Non-linearity Nonlinearity is an essential feature of the CAS (Rogers, Medina et al. 2005). In the non-linear system, the degree of change (input) is not correlated with the outcomes (output) of the system. A large stimulus to the system may exert a little or no influence on the output. The behavior of the system exceeds the sum of all individual's behavior. As a result, the system behavior may show features of randomness or chaos (Rouse 2000).

Emergent The agents in the system are intelligent; they can learn, gain experience and change their behavior accordingly. Because of the adoption and learning, behavior patterns emerge. Continual creativity is an inherent state of the system. In order to adapt to the changing environment, new elements, behavior, and idea will spring up in the system. It makes the system unpredictable.

Self-organization Self-organization is the unique characteristic of complexity science (Kaufmann, 1995; Holland, 1998). There is no central control in the system. A central body or master actor does not control other agents' individual activities. The outcomes of the system emerge from the influence of self-organization rather than central control.

2.4.4.3 Complex Adaptive System of Innovation

After elaborating on the characteristics of the CAS, it is useful to examine whether the innovation process is in line with the above characteristics.

Independent agents: Nowadays it's very difficult for companies to compete in the fierce environment without any connections. They are not isolated, rather than they are connected to other organizations to get access to external resources. This has been addressed in 2.2.3.

Non-linearity: Firms in the system innovate through collaborations built on complex relations with reciprocity and feedback mechanisms. The outcome of the innovation is not only affected by individual components, but also by relations between them. There are many feedback loops within the organization and among organizations.

Emergent: Different types of collective dynamics and new system properties emerge due to interactions amongst organizations (Schweitzer and Zimmermann 2001). The emergent properties not only depend on the organizations and their relationships but also on the external conditions, for instance, regulations, standards, market and so on. Scholar claims that the sectoral system of innovation is "a collection of emergent outcome of the interaction and co-evolution of actors and institutions (Malerba 2002)".

Self-organization: The interactions give rise to emergent properties that are the consequence of self-organization, which is the result of the system without central controller (Tapsell and Woods 2010). As learning leads to the adaption and new organizational structures and processes help organizations solve technological problems or gain competitive advantages, self-organization takes place (Rycroft and Kash 2004). Technological innovation is featured by self-organization process in companies and other organizations. The innovation network can generate new knowledge and recombine existing knowledge without the intervention of central control. Self-organization is more obvious in

the inter-organizational collaboration, especially in the high-tech industry, such as biotechnology and telecommunication (Richter 1994).

The matching four characteristics with CAS reveal that the innovation process can be considered as an adaptive, evolutionary process in the complex system. The key ability of success and survival are the adaptability and capability to learn and change. The recent research on the CAS provides a new basis for our understanding of how innovation actually occurs and how the factors influence it. The CAS models reveal the key process that underlies organizational learning and demonstrates the fundamental importance of dynamics and micro-diversity in the system (Allen 2001).

The CAS model of innovation represents a paradigm shift in the way we understand the interaction of innovation and social-economic development. The model transcends the prior models as it recognizes the importance of the collaborative knowledge creation and socio-economic environment. An increasing number of researchers have tried to explore the application of the CAS in the study of innovation, including the invention (Fleming and Sorenson 2001), the diffusion of innovation (Rogers, Medina et al. 2005), organizational learning (Carlisle and McMillan 2006), new product development (McCarthy, Tsinopoulos et al. 2006), and pharmaceutical industry (Smith 2012).

The most important tool for analyzing the complex adaptive model of innovation is the agent-based model using genetic algorithms or artificial neural networks. The simulation of the CAS model of innovation, executed on computers by defining a network of interacting rule-based components, produce a great number of data which can greatly expand our understanding of questions (Holland 1992).

2.5 Summary and Conclusion

Overall, we can conclude that innovation focuses on all activities, from basic research to the products. Knowledge is the foundation of innovation, while learning, as the core of innovation, generates new knowledge and improves current knowledge. Our understanding of innovation has evolved from linear model, non-linear model, and network model to systems model. The key points of this chapter are summarized as follows:

- Innovation gives rise to new products, production methods, management skills, and services, all of which are knowledge embedded in the organization. Companies need to improve existing knowledge for short-term competency, and create new knowledge for long-term competency.
- The process of the innovation is not linear. Instead, it is entirely non-linear, and has sub-processes that are connected by multiple loops. Through this, certain activities emerge as causes and effects, or consequences and prerequisites. Hence, the non-linearity unravels a key characteristic of innovation — uncertainty.
- The linear model is a simple illustration of the innovation process, while the nonlinear model also accounts for the uncertainty within the model. The network model incorporates interactions among different actors. But, these models are still incomplete in explaining the complexity of the innovation process.
- The systems approach of innovation adopts a holistic and interdisciplinary perspective. The 'holistic' nature is reflected by the system approach attempting to encompass the important determinants of innovation. Similarly, the approach is 'interdisciplinary' in that it integrates perspectives from various social science disciplines, including economics, sociology and regional studies (Fagerberg, Mowery et al.

2006). With the development of the SI, it also absorbs perspectives from nature and engineering disciplines, such as the evolutionary theory from biology and complex theory from engineering.

- The basic principle of the SI approach is that innovation does not take place in isolation. Relations are central to the innovation process. The systematic approach of SI addresses the innovation in a systematic way. The system of innovation is composed of various determinants, which interact with each other. The SI approach is becoming increasingly important for policy-makers to achieve their economic and social goals.
- The National Systems of Innovation (NSI) and the Regional Systems of Innovation (RSI) approaches use geographic delineations to characterize the systems. The Sectoral System of Innovation (SSI) approach focuses on certain sectors in terms of knowledge and products. Due to differences between the sectors, the dynamics of innovation also differ. The SSI provides a new methodology for analyzing innovation system. It is a heuristic method for understanding the complexity of technology change, innovation, and policy.
- In recent years, the complex adaptive innovation model that has emerged is rooted in complexity science. It is complex in that the system is a dynamic network of interactions, while it is adaptive because the individuals and collective behaviors evolve and self-organize according to the initial condition and the changing environment.
- With features of independent actors, non-linearity, emergence, self-organization, the complex adaptive system is a powerful way to describe the innovation system of the orphan drug in the US. The CAS is an important tool to understand factors that influence the evolution of orphan drug innovation system and to help policy-makers to formulate effective policies aiming at stimulating innovation.

Chapter 3 The Orphan Drug Act

3.1 Introduction

The innovation in the pharmaceutical industry has been significantly influenced by several legislations since the 1980s, including the Patent and Trademark Amendments (Bayh-Dole Act) in 1980, the Orphan Drug Act in 1983, and the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) in 1984 (Reichert 2003).

The Bayh-Dole Act of 1980 allows agencies to patent discoveries from government-funded research and license these patents for commercial use. The act has facilitated the transfer of knowledge from universities, small businesses and non-profit institutions to the industry. The Hatch-Waxman Act of 1984 was designed to prompt genetic research, since FDA approval for this can be obtained by submitting bioequivalence studies without conducting the costly clinical trials. It also offered an additional period of marketing exclusivity to cover the time a patented pipeline drug remained in development. The aim of Hatch-Waxman Act is to balance the incentives for encouraging innovation among drug companies with the opportunities for facilitating market entry by generic drug manufacturers. These two acts have demonstrated success in generating pharmaceutical innovation.

3.1.1 The Background of the Orphan Drug Act

Another important legislation is the ODA, which differs from the aforementioned acts by focusing on a particular set of diseases. The orphan drug is developed specially to treat rare conditions that, by definition, affect fewer than 200,000 people in the United States. The main obstacle to orphan drug development is the complex and costly FDA approval process (Pulsinelli 1999). Before 1962, drug approval was not as difficult as it is now, since drug

companies only had to demonstrate the safety and labeling the drug properly. After the amendment of Food, Drug and Cosmetic Act in 1962, efficacy was added to the drug approval process. Since then, the FDA had become more demanding before approving drugs, and drugs have had to cross more hurdles from the laboratory to the market. There are two main factors that cause the poor situation of orphan drug development before the ODA.

The Little potential for profitability

Drug development is a very costly and long process. It is estimated that obtaining drug approval takes 13.5 years and costs \$1,778 million on average (Paul, Mytelka et al. 2010). Drug companies need to recoup these costs via the sale of these products. Hence, most marketed drugs were developed to treat the common disease that affects a large number of people, and drug companies could only recover the cost of development from the large-scale sales of the drugs. The profitability of these drugs was reinforced with the patent protection, which entitles drug companies to take advantage of an exclusive market right (Pulsinelli 1999). The size of the market combined with patent protection determined the type of drug marketed and the ways drugs were marketed before the 1980s (Temin 1979). As making profit is the ultimate goal of the pharmaceutical industry, products with little prospect of commercial return had been neglected before the 1980s.

The difficulty in drug development

Moreover, it was difficult to develop drugs affecting few people. Firstly, although in some cases the small number of patients made orphan drug development less expensive and time-consuming than non-orphan drugs, the small number of patients made the design of effective clinical tests for orphan drug approval more difficult compared with non-orphan drugs. Most orphan drugs were not eligible for patent protection, so other companies can easily manufacture and sell the same drug without incurring drug approval. The competition among them would decrease profitability, which exacerbated the difficulty of recovering R&D costs. Before the Orphan Drug Act, without the

exclusive market rights and big market, the only one reason for drug companies to develop orphan drug was for public service (Goldman, Clarke et al. 1992).

3.1.2 The Birth of the ODA

While a single rare disease affects very few people, the total number of the people suffering from all the different rare diseases is huge. There are over 7,000 rare diseases affecting approximately 30 million US patients. Patients suffering from the rare disease should be given the same opportunity of receiving safe and effective treatments as other patients with more frequently occurring disorders. Therefore, the US government started to pay attention to solve this problem in the early 1980s. The National Organization for Rare Disease (NORD), led by Abbey Meyers, had played a very important role in promoting orphan drug legislation.

In 1983, President Ronald Reagan signed the United States Orphan Drug Act into law. The ODA is not only the outcome of collaboration between the industry and government, but it is also a good example of the influence of patient advocacy (EURORDIS 2008). Since then, it has become the most successful legislation in public health and has been the foundation of designing similar legislation in different countries. For example, legislations to improve drug development for the rare disease were introduced in Singapore in 1991, Japan in 1993, and Australia in 1997. The European Union passed orphan drug regulation in 1999, where Regulation No. 141/2000 is similar to the US ODA.

3.1.3 The Current Situation of the ODA

The ODA has successfully brought forth drugs for rare diseases in an unprecedented number and given hope to millions of patients. In the 25th anniversary of the US ODA in 2008, it is estimated that over 17 million people had benefited from orphan drugs in US (EURORDIS 2008); in the 30th

anniversary of the US ODA in 2013, over 400 orphan products were available to patients.

The management of the orphan drug is a challenging task for all countries. Although there are over 400 orphan drugs reaching the market, it is a very small number compared to 5000 rare diseases. As the number of orphan drug entering the market is increasing, the cost-effectiveness of the orphan drug needs to be consistently and transparently controlled via reasonable criteria.

In this Chapter, we firstly introduce the incentives offered by the 1983 ODA and a series of amendments after 1983. Then, the second section discusses the influence of the ODA in terms of the number of marketed orphan products, the expansion of biotechnology companies, and the development of personalized drugs. Thirdly, the ODA is controversial in terms of driving orphan drug innovation efficiently. Some limitations of the ODA are analyzed, including the high price of the orphan drug, and the repurposed orphan drug. Based on these limitations, the fourth section summarizes potential solutions for improvement of the ODA.

3.2 The Incentives of the ODA

Drug discovery and development is a long, uncertain, and expensive process. Hence, drug companies were reluctant to invest in R&D for rare diseases that affect a relatively small number of the population unless they can be assured of a good return on their investment. The ODA passed by Congress in 1983 has created political incentives to stimulate research organizations to participate in basic research on orphan drugs to treat rare diseases and support drug companies to invest in the development and marketing of the orphan drug.

The ODA has been beneficial not only to the patients suffering from the rare disease but also to innovation in pharmaceutical industry (Yin 2008). The development of the orphan drug has been on an ascendant trajectory since 1983. Only ten rare diseases had received FDA approval in the decade prior to 1983, and the total number of approved orphan drugs was 36. Since the launch of the ODA in 1983, hundreds of orphan drugs are available in this small market.

3.2.1 Market Exclusivity

The most influential incentive provided by the ODA is the seven-year period of market exclusivity for approved orphan drugs. Before the ODA, patent protection was the only way to protect the product from imitation and competition in the pharmaceutical sector. The Patent is the critical knowledge and financial resource for firms in the high-technology field. All the drugs that can be sold in the US market must obtain FDA approval, and the ODA protects orphan drugs by offering 7-year market exclusivity and refusing the approval of drugs treating the same rare disease.

Seven-year market exclusivity is different from the patent. It is believed to be a superior protection to the patent for orphan drugs (Dear, Lilitkarntakul et al. 2006). Firstly, it is easier to demonstrate the orphan status of a drug for market exclusivity than to demonstrate the novelty of the drug for patent. Some drugs are not eligible for patent protection as they have been synthesized and marketed before the understanding of their medical use, whereas they can get market protection if they are granted with the orphan designation. For example, albuterol, clonidine and caffeine are not eligible for patent protection but eligible for orphan drug market exclusivity. Secondly, patents are applied and awarded in the early stage of drug development, which wastes many years of patent protection in advance of drug commercialization. On the contrary, the market exclusivity of orphan drugs is valid from the date of FDA market approval without the loss of protective years on product development. Compared with patent protection, market exclusivity is easier to obtain and

more valuable to invest in, which leads to the trend of more designation application from biotechnology companies (Spilker 2002).

Market exclusivity is a significant incentive for companies who want to develop an orphan drug because the scale of the market and the price of the orphan drug would not be sufficient to recoup their R&D costs if there is no market protection. Market exclusivity makes the orphan drug profitable. On one hand, it can help drug companies to recover the cost of drug development, so this incentive provides motivation for manufacturer to develop orphan drug; on the other hand, the protection from competition allows drug companies to charge a monopoly price above the marginal cost and make enormous profits (Cuttler and Silvers 2010). This provision is also where most controversy arises, which will be elaborated in section 3.5.

3.2.2 Tax Credits

The second biggest financial incentive is that the ODA gives tax credits for half of the amount of money spent on clinical trials. In theory, 50% tax credit has stimulated orphan drug innovation by directly influencing the development cost margin (Yin 2008). The credit has decreased the cost of conducting human clinical trials, which tests the efficacy and safety of drugs for FDA approval and accounts for a large proportion of the total cost of drug development (DiMasi, Hansen et al. 2003).

The incentive of tax credits works under the condition that the company that develops the orphan drugs has the income from the sales of other products or from the commercial distribution of unapproved orphan drugs (Seoane-Vazquez, Rodriguez-Monguio et al. 2008). However, the provision of tax credits does not match the nature of drug development in the biopharmaceutical industry, which make this incentive less effective (Pulsinelli 1999). On one hand, the process of drug development includes human clinical trials and animal trials, but the tax credit does not apply to the latter one that is sometimes as

expensive as the former one. On the other hand, the credits cannot be carried backward and forward. This provision is only valuable for firms with taxable profits, which is a particularly important problem for biotechnology firms. The majority of biotechnology firms do not possess revenue-generating products or the tax liability for a long period, so the 50% tax credits do not work for these companies.

3.2.3 Orphan Products Grants

The Orphan Products Grants Program provides funding for the clinical studies on the safety and/or effectiveness of products for rare diseases or conditions, where there is no existing therapy or the funded product superior to the existing treatment. The grants in the 1983 Act only defrayed the cost of clinical tests, while the Amendments in 1988 extended the grant coverage to all the tests. The grants have supported the orphan product development in a timely manner and with a very modest investment. The program supports clinical studies for up to three years for Phase I trial and up to four years for Phase II and III trials. There are normally 60-85 ongoing grant-funded studies, and the majority of them are multi-year grants approved in the prior year.

The Orphan Products Grants is the FDA's largest grants program. The OOPD engages in this program (Goodman 2010). Before providing funds, the OOPD reviews the grant application to check whether the program requirements are satisfied and convene peer review panel to select the best scientific proposal. After that, the OOPD conducts tests to guarantee that the products meet the requirements of the regulation and program. Moreover, it monitors the grant-funded projects to minimize the risk of violations in human subject's protection requirement.

Table 5 The Budget of Orphan Products Grants Program from 2007 to 2011

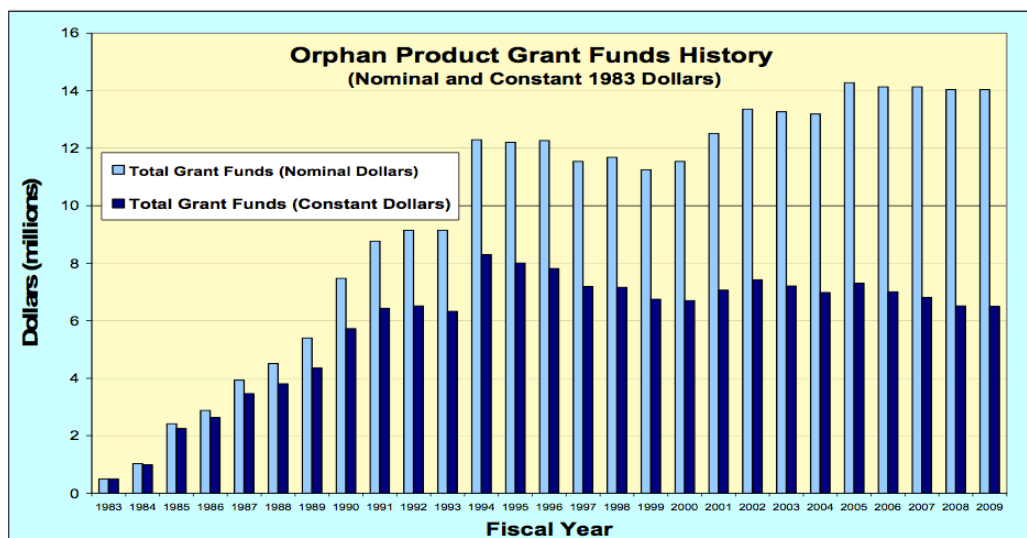
	Orphan Product Grants	Pediatric Consortia Grants	Program Administration	Program Level
FY 2007 Appropriation	\$14,035,060	0	\$3,033,156	\$17,167,256
FY 2008 Appropriation	\$14,035,060	0	\$3,656,101	\$17,691,161
FY 2009 Appropriation	\$14,035,060	\$2,000,000	\$3,805,000	\$19,840,060
FY 2010 Appropriation	\$14,035,060	\$3,000,000	\$5,074,741	\$22,785,290
FY 2011 Appropriation	\$14,035,060	\$3,000,000	\$6,643,628	\$23,678,688
FY 2012 Appropriation	\$14,035,060	\$3,000,000	\$6,601,140	\$23,636,200
FY 2013 Appropriation	\$12,960,744	\$3,000,000	\$7,179,153	\$23,139,897
FY 2014 Appropriation	\$14,035,060	\$3,000,000	\$7,710,105	\$24,745,165
FY 2015 Appropriation	\$14,035,060	\$3,000,000	\$6,563,940	\$23,599,000

(Data Source: OOPD Annual Budget Report)

The amount of appropriated funds is typically approximately \$14 million for a given fiscal year. The major portion goes towards the continued funding of previously approved grants. For instance, Orphan Grants Program supported 22 new clinical studies and about 40 continued studies of prior approved grant in FY 2009, with a total funding of \$14,035,060 (Table 5). In FY 2014, 15 new grants were awarded (out of 99 grant applications), and the grants program also continued support for approximately 60 other ongoing clinical projects.

Since the inception of this program, OOPD has received more than 1800 applications, reviewed over 1400 applications and funded over 700 clinical studies. More than 55 orphan products approved by FDA for marketing are supported by the Orphan Grant Program, and approximately 10% of the orphan product approvals are funded by this program (FDA 2016). A number of outcomes from the funded research have been published in peer-reviewed journals, which has contributed a lot to the health of people suffering rare diseases worldwide. The achievements have demonstrated that the Orphan Products Grants Program has successfully fostered and stimulated the

development of promising discoveries into new safe and effective products for rare diseases.



(Data Source: FDA)

Figure 10 The Orphan Drug Funds History from 1983 to 2009

However, the Grants have been contributing less to the cost of conducting clinical tests. On the one hand, as shown in Figure 10, there is a steady increase of Grants from 1983 to 1994, as the amount adjusted for inflation started to decrease from 1995. Since 2005, the nominal value of the Grants has kept at \$14 million with a slight decrease. On the other hand, the rapid increase in the cost of clinical trials and the complexity of clinical trial design for the orphan drug has decreases the number of new OOPD grants. From 1995, the number of new grants has decreased and maintained at around 20 (Figure 11). For instance, FDA funded 16 and 18 new clinical studies in FY 2014 and FY 2015, respectively.

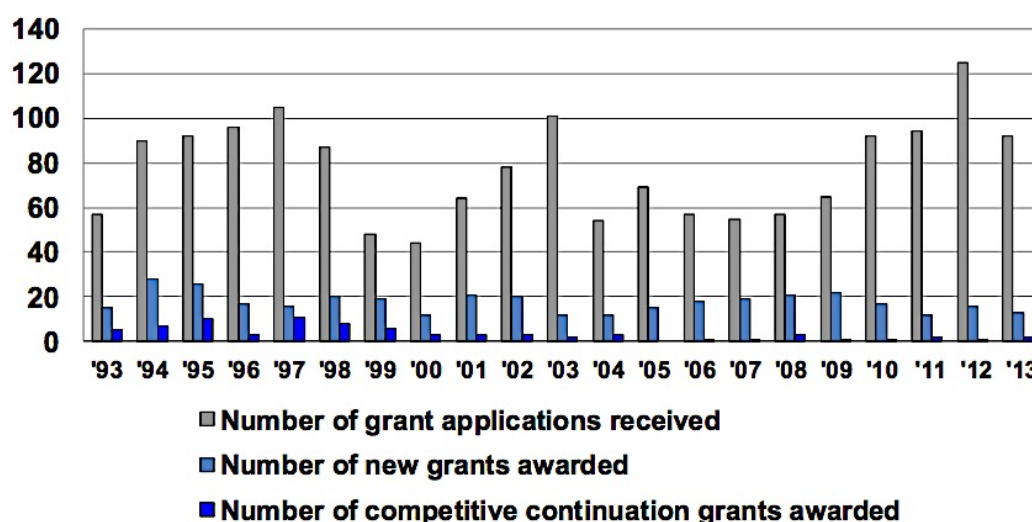


Figure 11 The Annual Number of the Grant Applications and Awards from 1993 to 2013

3.2.4 Assistances in Clinical Trial

Due to the high complexity and cost of FDA approval, drug companies have faced too many uncertainties to secure the approval. FDA provides direct assistance for sponsors to facilitate the process of approval by providing the information about the kind of tests drug companies need to complete and providing guidance on preparing the dossier. These supports are especially helpful for orphan drug development, as these drugs target so few people that drug companies have few resources and experience in designing clinical trials.

The OOPD in FDA keeps a close relationship with research organizations, patient advocacy groups, and other government agencies. It helps the sponsors in providing expertise about clinical trial design and review. The OOPD also provides training courses for drug companies on orphan drug discovery and development. The strong communications between companies and FDA lead to the increase of the successful outcomes (Pariser 2010). Due to the scarce resources of organizing clinical trials, FDA provides flexibility to the orphan drug development. The FDA reviews the clinical data and makes the decision on orphan drug approval in a flexible manner; some drugs are approved without fully performing the clinical trials.

3.2.5 Fee Waivers

The program of fee exemptions and waivers was started in 1992 under the PDUFA (Prescription Drug User Fee Act). The PDUFA authorizes FDA to collect fees from drug companies, and directs FDA to waive and reduce fees under certain circumstances, such as when paying fee is an obstacle to innovation because of the limited resources available to sponsors, or when the fees to be paid will be more than the expected costs of reviewing drug application or when it is necessary to protect the public health through fee exemption and waiver. There are three types of user fees: application Fees, establishment Fees, and product fees.

Application Fees

In FY 1998, the application fees exemptions were added. These exemptions are automatic and do not require waiver requests. As a result, designated orphan products are given automatic exemptions from application fees.

Product and Establishment Fees

From FY 2008, PDUFA offered the exemptions from product fees and establishment fees for certain approved orphan drugs. The designated orphan drug product is exempt from the product and establishment fees when it meets the public health requirements. However, drug companies must have less than \$50 million in gross worldwide revenue in the year preceding the application for the exemption. Table 6 summarizes the exemptions granted by FDA from FY 2007 to FY 2011. The total value of the exemption for orphan products reached \$ 67 millions in FY 2011.

Table 6 The Exemptions for Orphan Products

	FY2007	FY 2008	FY 2009	FY 2012	FY 2011
Orphan Product	21.3	27.8	23.8	21.8	32.5
Previously Submitted	4.5	4.0	7.5	4.0	5.0
Total Exemptions	25.8	31.8	31.3	25.8	37.5
Total Value of Exempted Application Fees	\$23,077,150	\$37,401,500	\$38,975,000	\$36,191,625	\$57,825,000
Orphan Product Fee Exemptions		14	16	27	27
Value of Product Fee Exemptions		\$910,420	\$1,144,320	\$2,152,440	\$2,336,040
Orphan Establishment Fee Exemptions		5.24	7.45	11.49	13.79
Value of Establishment Fee Exemptions		\$2,056,963	\$3,169,869	\$5,252,314	\$6,857,382
Total Product and Establishment Fee Exemptions		\$2,967,383	\$4,314,189	\$7,404,754	\$9,193,422
TOTAL Value of Exemptions	\$23,077,150	\$40,368,883	\$43,289,189	\$43,596,379	\$67,018,422

3.2.6 Open Protocols

Another way the ODA stimulates drug innovation is the open protocol for clinical trials. The provision is applied for designated orphan drugs that are in the stage of clinical tests and are available to the patients participating in the clinical test. This provision helped drug companies to get more clinical test data as well as recoup part of the cost via selling drugs before passing FDA approval. It is not only an incentive to drug companies but also a benefit for patients. The patient can gain effective treatment as early as possible.

3.2.7 Protocol Assistances

The protocol assistance is a special form of scientific advice during the development process of orphan medicinal products. It allows drug companies to get answers to questions about the types of studies needed to demonstrate the drug's quality, benefits and risks. In addition to the scientific advice, companies can also receive answers to the questions relating to the criteria for approval.

The ODA gives formal protocol assistance when orphan drug sponsors request for it. The sponsors do not need orphan drug designation to receive protocol assistance. It is an important support for the orphan drug development taking the unique challenges associated with developing these products into accounts. However, due to the changes in the FDA regulations and the rules of Investigational New Drug, and New Drug Application process, the protocol assistance is seldom used in the US (Shah 2006).

Overall, the ODA consists both market-pull and technology-push incentives to reduce the cost of drug development and increase the possibilities of making profits by market protection (Milne and Tait 2009). As shown in Figure 12, these incentives support orphan drug innovation in multiple ways and benefit various actors in the drug R&D processes. Both large and small companies benefit from seven-year market exclusivity; tax credits are more valuable for drug companies which have revenues than for start-ups without marketed products generating revenues; orphan drug grants and fee waivers are more favorable to small biotechnology companies with financial strains; clinical trial assistance is more favorable to small companies because the lack of experience in drug development.

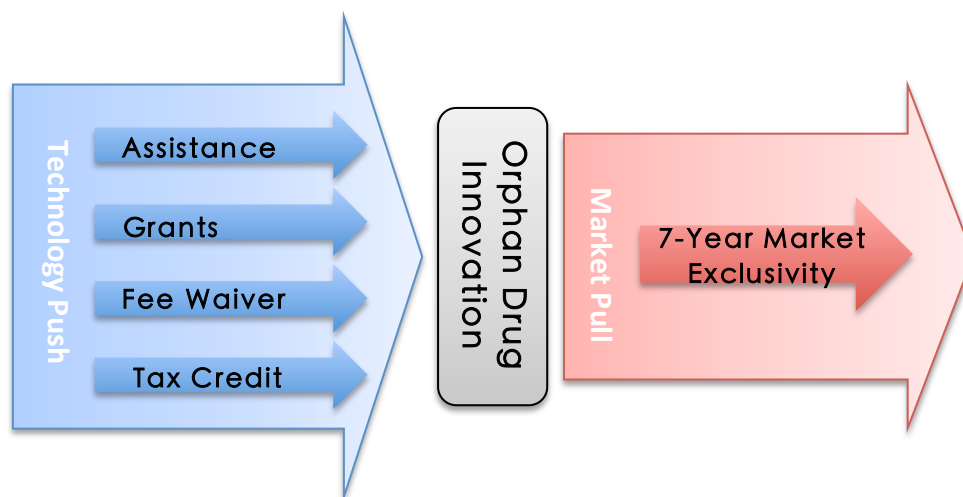


Figure 12 The Incentives of the ODA

3.3 The Orphan Drug Act Amendments

All the incentives in the 1983 Orphan Drug Act have encouraged drug companies to develop new drugs or new indications of existing drugs to treat rare diseases. However, since 1983, the ODA has faced a lot of challenges in the process of the implement. The US Congress had concerned with these perceived problems and tried to solve them in the ODA Amendments.

3.3.1 The 1984 ODA Amendment

In the 1983 Act, a rare disease was defined as any diseases or conditions that affect very few patients that drug companies cannot recover the cost of drug development from the sale of drugs. The vague definition made drug companies provide production-cost documents and share sensitive information with the FDA (Pulsinelli 1999). The 1983 act did not get an overwhelming response since drug companies were reluctant to share their information. As a result, Congress passed the 1984 ODA Amendment that enlarged the definition of rare diseases to include diseases affecting fewer than 200,000 people in the US. During the five months after the amendment, the number of orphan designations granted by the FDA increased from 22 to 53. According to this definition, the Office of Rare Diseases Research (ORDR) listed 6845 rare diseases. There are approximately 250 new rare diseases included in rare disease category each year (WÄStfelt, Fadeel et al. 2006).

3.3.2 The 1985 ODA Amendment

The most significant change to the 1985 Amendment was the new requirement of orphan drug designation. One of the requirements for designation in the 1983 ODA was that the drug must be unpatented or un-patentable, which created many problems in some cases. For instance, some drugs were patented, but the patent would expire in no more than seven years, these drugs were not qualified to apply the designation according to the 1983 Act. In addition, it was

very difficult to distinguish between a patentable drug and un-patentable drug. Congress resolved this problem by simply removing this requirement. Therefore, FDA can provide market exclusivity to both patented and unpatented orphan products. Thus, orphan drug designations are granted independent of the patent system (Wellman-Labadie and Zhou 2010).

This amendment also extended orphan status to antibiotics and established a National Commission on Orphan Diseases to assess the public and private sector efforts on developing and marketing orphan drugs (Asbury 1992). The 1985 ODA amendment also expanded the availability of grants to support all 'qualified testing' rather than 'qualified clinical testing' and increased the duration of funding to more than 3 years.

3.3.3 The 1988 ODA Amendment

The 1988 Amendment did not have the significant influence that previous amendments did, since most simply corrected minor errors (Pulsinelli 1999). However, one of the changes is that sponsors can apply for the orphan drug designation at any time before the submission of the application for drug marketing approval. This change allowed sponsors to apply orphan drug designation for any unapproved use of the drug with or without previous marketing approval for other indications (Seoane-Vazquez, Rodriguez-Monguio et al. 2008). Many orphan drugs were previously launched as non-orphan drugs or currently in the process of non-orphan drug approval, and they were later granted marketing approval for treating rare diseases. Nearly half of the blockbuster drugs with orphan designation had been launched before (Wellman-Labadie and Zhou 2010).

3.3.4 The 1993 ODA Amendment

1993 ODA Amendment focused on the orphan drug designation. It established the process of application, specified the documents required for the application and explained how two drugs were considered same or different for the purposes of market exclusivity.

These amendments do not change the main incentives of the ODA, but make the legislation clearer and orphan drug innovation more attractive to drug companies through the new definition of rare disease and the new requirements for the orphan drug designation.

3.4 The Influence of the Orphan Drug Act

It is obvious that the ODA has played an important role in motivating drug companies to bring rare disease treatments to the market. But, it has also nourished many biotechnology companies.

3.4.1 The Number of Approved Orphan Drugs

Since the launch of the ODA in 1983, over 400 orphan drugs have been marketed, and the ODA has been successful in bringing products to market for people suffering rare disease.

From Figure 13, FDA has approved 34 new products that included 13 orphan drugs (9 NMEs, 4 BLAs) in 2009. In 2012, more than 50% of newly approved drugs were orphan drugs. With more orphan drugs available to patients, the healthcare of rare disease patients improved to a large extent.

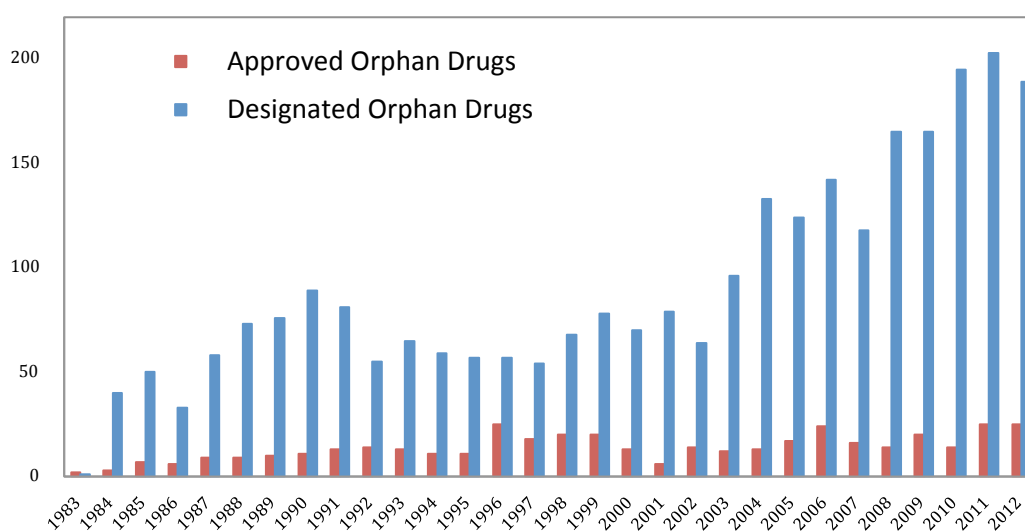


Figure 13 The Number of Designated and Approved Orphan Drugs from 1983 to 2012

Someone believes that the successful approval of a drug would stop further innovation activities in the same area, which is not true for the orphan drug. In contrast, in some cases, once an orphan drug has been approved, another orphan drug would get designated, such as the treatments for Gaucher disease which had five orphan drugs approved (Table 7).

Table 7 The Development History of Orphan Drugs treating Gaucher Disease

Name	Compound	Company	Approval date in US	Therapeutic class
Ceredase	Alglucerase	Genzyme	1991	Enzyme
Cerezyme	Imiglucerase	Genzyme	1994	Enzyme
Zavesca	Miglustat	Actelion Pharmaceuticals	2003	Substrate reduction
VPRIV	Velagluceras e alfa	Shire Plc	2010	Enzyme
Ellelyso	Taliglucerase alfa	Protalix, Pfizer	2012	Enzyme

3.4.2 The Growth of Biopharmaceutical Sector

The ODA has been beneficial not only to the patients suffering from rare diseases but also to the innovation in the pharmaceutical industry (Yin 2008). The ODA has successfully attracted the interests of the pharmaceutical industry to develop drugs for rare disease patients by creating incentives for companies to support R&D and marketing.

There are two main manufacturers in the biopharmaceutical industry, namely pharmaceutical companies and biotechnology companies. While large pharmaceutical companies have traditionally thrived on blockbusters, biotechnology firms have played an important role in orphan drug innovation. However, because the blockbuster model is less effective, pharmaceutical companies have started to consider orphan drugs seriously to strengthen their R&D pipeline. For instance, Pfizer signed an agreement with an Israel biotech company Protalix at the end of 2009 to develop and commercialize its drugs for Gaucher Disease that affects 1 in 50,000 to 1 in 100,000 people.

In Table 8, the top 10 pharmaceutical companies accounted for half of the orphan drug sponsored by pharmaceutical companies. For instance, Pfizer, Novartis, Johnson & Johnson, GlaxoSmithKline, AstraZeneca, and Roche had contributed over 25 orphan designations. 50% of orphan drug approvals were obtained by biotechnology companies, among which Amgen (14 approved orphan drug), Genzyme and Genentech (9 and 8 approved orphan drugs each) were the most active companies. The earlier stage of orphan drug R&D is usually undertaken by small-sized start-up biotechnology companies, while larger pharmaceutical companies focus on the late stage drug development and marketing, however, there are still few very large Big Pharma conducting early-stage research and development of orphan drugs (Villa, Compagni et al. 2009).

Table 8 FDA Orphan Drug Approvals by Pharmaceutical Companies and Biotechnology Companies

Rank	Company	2007 Revenue (US\$ million)	Orphan designation	Designated branded	Orphan approval
1	Pfizer	44,424	36	25	9
2	GlaxoSmithKline	38,501	41	27	18
3	Sanofi-Aventis	38,452	14	4	3
4	AstraZeneca	28,713	31	16	5
5	Merck	26,532	8	6	3
6	Novartis	25,477	50	34	21
7	Johnson & Johnson	24,866	48	35	7
8	Roche	21,988	25	22	7
9	Eli Lilly	17,638	9	7	4
10	Wyeth (acquired by Pfizer in 2009)	17,179	14	11	7
Top 10 Pharma Total			276	187	84
Pharmaceutical Total			541	382	175
1	Amgen	14,771	33	18	14
2	Genentech (acquired by Roche in 2009)	11,724	23	19	8
3	UCB SA	4972	7	1	0
4	Gilead Sciences	4230	6	3	2
5	Genzyme	3814	35	19	9
6	Biogen Idec	3172	23	8	1
7	CSL Ltd	2788	8	5	1
8	Cephalon	1773	14	11	3
9	Celgene	1406	17	12	5
10	Actelion	1098	8	6	3
Top 10 Biotech Total			174	102	46
Biotechnology Total			1461	688	177
Grand total		2002	1070	352	

(Source: Wellman-Labadie and Zhou 2010)

The smaller number of orphan drugs developed by pharmaceutical companies can be attributed to the priorities of developing drugs for larger patients to make bigger profits. In addition, the ODA incentives are extremely appealing for start-up biotechnology companies. For instance, Genzyme is the first-generation biotechnology company. Ceredase, the first orphan drug for patients with Gaucher disease receiving FDA approval, is also the first product of the Genzyme. In 2010, Genzyme became the world's third-largest biotechnology company, and it was acquired by Sanofi-Aventis in February 2011. There are very few small biotechnology companies with non-orphan products, which can also be explained by the characteristics of these companies (Seoane-Vazquez, Rodriguez-Monguio et al. 2008).

The Growth of Genzyme

Ceredase is produced by Genzyme as a treatment for Gaucher disease. This is a rare genetic disorder where patients cannot produce the essential enzyme, glucocerebrosidase, to break down fat deposits in cells. The basic research about Gaucher conducted from the mid-1970s to the early 1980s by NIH and

other research organizations led to the discovery of alglucerase, which is a man-made enzyme replacing the missing enzyme of Gaucher disease.

Like any other drug company, Genzyme faced big risks of drug development. Even after obtaining FDA approval, these drugs may not be profitable, because they may face competition from similar drugs and alternative treatments. The ODA is of great significance for the birth of Ceradase, which was believed with the limited potential market and not qualified for patent protection (Goldman, Clarke et al. 1992). Genzyme launched clinical trials in 1984 and got FDA approval for alglucerase with trademarks for Ceredase in 1991. Its total R&D cost was \$58 million, and the sales of Ceredase were \$39.6 million in 1991. Three years later, Genzyme introduced Cerezyme that is the second-generation product of Ceradase. Cerezyme cost \$200,000 per patients per year. It is now still a very important treatment for Gaucher disease and the biggest moneymaker of Genzyme.

3.4.3 The Global Influence of the Orphan Drug Act

One of the significant influences of the ODA is that it provides the successful model for other countries to design the similar legislation. Based on the successful experience in the United States, European Union established Orphan Drug Regulation in 1999 with the aim to promote the development of drugs for patients suffering from rare diseases. Singapore in 1991, Japan in 1993, Australia in 1997 established orphan drug legislation and many other countries are planning the introduction of orphan legislation.

The European Union passed orphan drug regulation in 1999, similar to the ODA in the US. The ODA provides six main incentives for drug companies to bear the high cost and risk of orphan drug development. From Table 9, we can see there are several differences between them. The designation and marketing exclusivity of orphan drugs are governed at the European Union level, but other government intervention decisions are the member state's responsibility

(Denis, Mergaert et al. 2010). For example, the tax in the Europe is controlled by individual member states, so the implementation of the tax credits is not possible in the extensive range of Europe. Moreover, orphan drug research also lacks sufficient funding. The difference between the tax credit and grants may explain why the number of orphan drugs is higher in the US than Europe (Dear, Lilitkarntakul et al. 2006).

Table 9 The Comparison between the US and Europe orphan drug development

	Europe	The US
Date of Legislation	2000	1983
Definition of Rare Disease	<5/10000	<7.5/10000
Incentive		
Market Exclusivity	10 years (reviewed after 5 years)	7 years (not reviewed)
Others	Fee reduction, protocol assistance	
Tax Credit		50% Tax credit for the clinical test, and the research grants for orphan disease
The Number of orphan drug designations to 2015*	Total number 1596** 99.75 per year	Total number 3633*** 110.10 per year
The Number of drugs with market approval to 2015*	Total number 114** 7.13 per year	Total Number 552*** 16.73 per year

* 30 December 2015

**European orphan drug data: http://ec.europa.eu/health/documents/community-register/html/index_en.htm

***US orphan drug data: <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>

Some orphan drugs were marketed in both EU and the US, but there is a time lag of marketing between the two regions. For instance, Stiripentol, an orphan drug used to treat Dravet Syndrome, received orphan designation from FDA in 2008, but it was approved by the European Medical Association two years earlier than the US; while Cerezyme received FDA approval in 1994 and European approval in 1998.

In 2007, the US and European drug regulatory agencies started to adopt the same orphan designation application forms for both agencies. This approach simplifies and accelerates the process for sponsors seeking orphan drug designations in both the US and Europe. Now, about 50% of the orphan designation applications submitted to the EMA are done in parallel with the FDA, and about 30% to 40% of the applications used the joint FDA-EMA application forms (Mariz, Reese et al. 2016). The joint orphan designation application has enabled patients with rare disease to get access to the treatments as early as possible regardless of whether they are in the US or Europe.

3.5 The Limitation of the ODA

As the number of the orphan drugs reaching the market is increasing, a lot of attentions have been paid to the limitations of the current ODA. These limitations have been viewed as a shortcut to faster market approval for drugs with longer monopoly rights. For instance, the high cost of treatments, which needs to be consistently and transparently controlled via the reform.

36% of orphan drug approvals are used to meet the needs of patients suffering from rare cancers, and 1% of drugs were withdrawn after approval (Stockklauser, Lampert et al. 2016). The accessibility and availability of orphan drugs are questionable. There was approximately US\$ 60 billion in sales for a relatively small patient population, and patients paid twice for the drugs as the public funds for supporting R&D as well as the cost of treatments (Wellman-Labadie and Zhou 2010). Moreover, in order to subsidize the lower price in other countries, drug companies have to increase the drug price in the US market. NORD complains that the ODA is too protective of the companies that are the first to obtain FDA approval. The goal of the legislation is to ensure that

drug companies make a reasonable profit on orphan products, rather than yielding enormous profits.

3.5.1 The Market Exclusivity

The most important and controversial incentive provided by the ODA is the seven-year period of market exclusivity for orphan drugs.

All the drugs that can be sold in the US must be authorized by FDA. Without the patent protection, the ODA protects orphan drugs by refusing the approval of other drugs that treat the same rare disease. The price of drugs under market protection is higher the marginal cost due monopoly by pharmaceutical companies (Cutler and Ericson 2010). Market exclusivity is an effective way to help companies recoup their R&D costs and encourage innovation, but this is also where the controversy stems from. One criticism concerns the high cost of some orphan drugs, which is called 'blockbuster' orphan drugs that have huge profits generated from the ODA market protection.

High Profit to Companies

From 2001 to 2005, the sales of biopharmaceutical drugs including a number of orphan drugs, increased by 127% in the US, 158% in the UK, 227% in France and 235% in Germany (Danzon and Furukawa 2006). There were 43 brand name drugs with orphan designation having annual global sale over US\$ 1 billion and 33 orphan designated drugs with annual global sales between US\$ 100 and 999 million in 2008; among these 43 blockbusters, 18 drugs had single designation, 15 drugs had two designations, and 10 drugs had 3 or more orphan designations (Wellman-Labadie and Zhou 2010).

The market exclusivity provision has demonstrated to be quite polemical, and it has created the problem of market inefficiencies. From an economic standpoint, some drug companies take advantage of this provision to earn immense profits

from their products. For example, AZT for HIV/AIDS, Pentamidine isethionate for pneumonia associated with AIDS, human growth hormone for the improper growth of children short of the enzyme and Ceredase for Gaucher disease, are four drugs that had recouped the costs of their development from their within the initial one or two years (Pulsinelli 1999). Furthermore, the annual global sales of 11 orphan products exceeded US\$ 100 million in 2008 (Wellman-Labadie and Zhou 2010). These results from the market protection will lead to the loss of society (DiMasi, Grabowski et al. 2004).

Table 10 The Most Expensive Orphan Drugs

Product	Company	OD Indication	Cost per year (US Dollar)
Soliris	Alexion	Paroxysmal nocturnal hemoglobinuria, PNH	409 500
Elaprase	Shire	Type II Mucopolysaccharidoses	375 000
Naglazyme	Biomarin	Type II Mucopolysaccharidoses	365 000
Folotyn	Allos	Lymphoma peripheral T cell	360 000
Cinryze	Viropharma	Hereditary angioedema	350 000
Myozyme	Genzyme	Pompe	300 000
Arcalyst	Regenero	Cryopyrin associated periodic syndrome	250 000
Ceredase/Cerezyme	Genzyme	Type I Gaucher disease	200 000
Fabrazyme	Genzyme	Fabry disease	200 000
Aldurazyme	Genzyme/Biomarin	Type I Mucopolysaccharidoses	200 000

As shown in Table 10, there are 9 orphan drugs with the cost per patient per year over US\$ 200,000. For example, Soliris, used to treat a rare kidney condition, costs over US\$ 0.4 million annually, making it the most expensive orphan drug worldwide. Although only 4000-6000 patients in the US use it, Soliris has brought over US\$ 500 million revenue to the drug company, Alexion.

In addition, the price of many orphan drugs approved in the US did not fall after the expiration of market exclusivity (Roberts, Herder et al. 2015). Generic orphan drugs are rare (Seoane-Vazquez, Rodriguez-Monguio et al. 2008), so the

price of lots of orphan drugs remains extremely high even after the 7-year market exclusivity.

Overall, the current pricing framework of orphan drugs is not based on the drugs' performances but on monopoly rights offered by the ODA. Some suggestions are given to modify the ODA to encourage competitions, as market forces will result in lower prices.

Limited Availability of Patients

The protection from competition allows drug companies to charge a monopoly price, and orphan drugs are usually very expensive. Private insurance does not cover 100% of the cost, and there are 47 million people uninsured who are excluded from the ODA benefit in the US. (EURORDIS 2008). Moreover, the increasing price of drugs is putting orphan drugs beyond the reach of many people. Because there is usually no alternative, the access to orphan drugs is influenced by the affordability for rare disease patients.

The ODA does not deal with the cost of drugs. According to the orphan drug report from EvaluatePharma, the average cost per patient per year in 2014 for an orphan drug was \$111,820 versus \$23,331 for a non-orphan drug. "Orphan drugs are usually very expensive and private insurance doesn't cover 100% of the price" and "moreover there are 47 million uninsured people in the US who are completely left out", explained by Abbey Meyer in the 25th anniversary of the ODA (EURORDIS 2008).

The Low Cost of Development

From Figure 14, it is obvious that compared with non-orphan drugs, orphan drugs are characterized with shorter clinical development times and higher possibility of FDA approval.

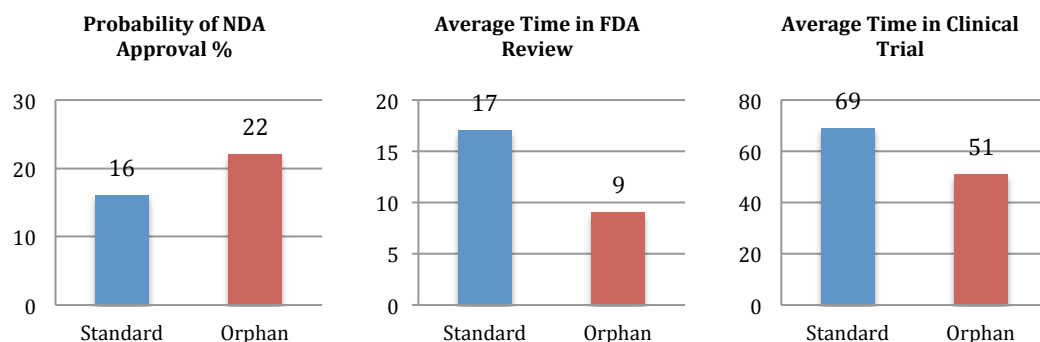


Figure 14 The Drug Development: Standard vs. Orphan Drug

According to EvaluatePharma, the cost of Phase III clinical trial is approximately half of the cost of non-orphan drugs at US\$103 million, compared to US\$193 million for a non-orphan; and with the 50% tax credit offered by the ODA, the cost could be at \$51m that is only a quarter of non-orphan drugs (Hadjivasiliou 2015). That means in some cases R&D cost of orphan drugs is lower than non-orphan drugs, which indicates that drug developer does not have to recoup the lower costs from the very high price of orphan drugs.

3.5.2 Other Problems Caused by the Orphan Drug Act

The Old Orphan Drug

Many orphan drugs are identified from the studies of diseases affecting a large patient population. Some orphan drugs are not originally developed to treat diseases with the small patient population. Firstly, many orphan drugs have been proved to be effective at treating more than one rare disease. Secondly, some orphan drugs are extended to treat common disease. Thirdly, several drugs whose initial indications are for common conditions can be developed for an indication of the rare disease.

For example, the FDA approved the new version of colchicine (brand name: Colcrys) as a treatment for Familial Mediterranean Fever (FMF), and the drug developer received 7-year market exclusivity. Colchicine is not new, because the plant from which colchicine is derived was first used to treat gout over 3000

years ago in ancient Greece, and the tablet of colchicine has been widely used as a generic prescription drug in the US since the past century. But, due to some historical reasons, colchicine has never been evaluated by FDA. After FDA approval, the drug developer sought to remove any other versions of colchicine from the market and increased the price by 50 times from \$0.09 TO \$4.85 per pill (Kesselheim and Solomon 2010). The raised price has a big influence on the availability of drugs to patients with gout and FMF.

This story reveals a major limitation of the ODA. The market protection as an incentive to attract drug R&D is not taking into consideration the real value and quality of the product. To discover new uses of an old drug should be encouraged, but the improvement of public health is the ultimate goal in encouraging it. In this case, Colcrys does not show a big improvement in the patients, but rather increases the burden of patients or insurers. Policymakers should address this problem, otherwise it would bear considerable costs.

Considering potential profits, the repurposing of an established drug for treating another disease has become an attractive strategy, especially in the orphan drug area (Sardana, Zhu et al. 2011). The tolerance of the high price is based on the small market of the orphan drug. But, for the repurposed orphan drugs, the price should only reflect the cost of secure and safe production, not anything else.

The uneven distribution of orphan drug R&D

Although a fundamental process has been made so far, there are over 7000 rare diseases in the US and only 500 of them have got an approved therapy (Figure 15). These drugs cover only 8% of 7000 rare diseases, and nearly 1/3 of approved orphan drugs are oncology-related products. From that, we can see the distribution of orphan drug development is uneven. Many efforts must be put into the neglected rare diseases to meet the needs of all the patients.

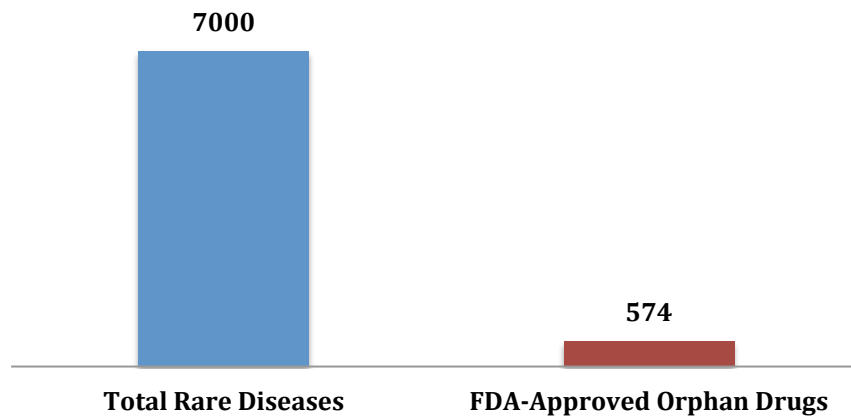


Figure 15 Number of Orphan Diseases vs. Number of FDA Approved Orphan Drugs

Moreover, the small number of patients is an obstacle for the clinical evaluation of orphan drugs. Some orphan drugs are adequately tested before being brought to market, while others are not. FDA approved Wellstat Therapeutics' uridine triacetate based on a 4-patient trial for the treatment of hereditary orotic aciduria (HOA), which is a very rare indication with 20 patients reported worldwide (Mullard 2015).

Altogether, the abuses of the ODA made the orphan products enjoy enormous sales under the protection of the legislation designed to stimulate the development and marketing of drugs with limited commercial value. The abuse of the incentives in the ODA will threaten its future (Asbury 1985). Since the objective of the ODA is to encourage the development of drugs for patients with rare diseases, it is very important to make sure that the ODA does not seem to contribute to the health care costs.

3.6 The Proposed Solution for the ODA

The limited availability, high price, and unknown safety effects illustrate that the policy of orphan drug faces challenges. The pricing and reimbursement of orphan drugs are a high priority issue for policy-makers, legislators, academics

industry leaders and patients (Simoens 2011). Several solutions have been proposed to enhance the availability of orphan drugs for rare disease patients. As described in the ODA, 'patients with rare diseases have the same right to effective therapies as those with more common diseases'. The core principle of the ODA is to provide 'non-economic societal values' for patients of rare disease to get access to therapies. The solutions should balance the interests of patients, regulators, payers, and shareholders.

Several proposals have been put forward to change the duration of market exclusivity. The Orphan Drug Amendment of 1992 proposed reducing the period of exclusivity to 2 years and withdrawing the exclusivity if the total revenue exceeds \$200 million at any time in the next seven years. The Biotechnology Industry Organization (BIO), an organization for protecting biotechnology companies, advised to reduce the seven-year market exclusivity to five years and allow drug companies to apply for another five-year protection if the drug has limited commercial potential. The proposal of 1994 Amendments tried to cut the duration to four years and gave the opportunity for the drug companies with limited commercial value product to apply for another 3 years. But, the 1992 and 1994 amendments were not brought to vote in Congress and the BIO proposal was not even introduced to Congress. But, biotechnology and pharmaceutical companies that operate with the motivation of profit-maximization seem reluctant to invest in R&D for rare diseases if they are not sure whether they can benefit from the incentives of the ODA.

The mechanism of orphan drug program in Japan can be considered as a good example. Drug companies in Japan have to pay 1% sale tax on the orphan drugs with over 100 million annual profits until all the funding provided by the government has been repaid (Cheung, Cohen et al. 2004). The program has not had a negative influence on stimulating orphan drug development as over 100 orphan products have been approved since 1993. It is a good way to provide funding for unprofitable drugs and revoke the funding paid for profitable orphan drugs.

3.7 Summary

Rare diseases have had a profound impact on rare disease patients. However, the small market of the orphan drug is the main obstruction to its development. With the aim to address the critically unmet medical needs of rare disease patients, President Ronald Reagan signed the Orphan Drug Act into law in 1983 to encourage the development of orphan drugs.

The influence of the ODA is not only in the area of offering the treatments for the patients suffering from the rare disease but also in nurturing the expanding biotechnology sector and providing a model for other countries to enact the similar legislation. The influence of the act has spread to other countries. Notably, laws were introduced to improve drug R&D for rare diseases in Singapore in 1991, Japan in 1993 and Australia in 1997.

The success of the ODA in encouraging the innovation of hundreds of orphan drugs is undeniable, but the high cost of treatments makes it controversial. Since the objective of the ODA is to stimulate the development of drugs for patients with rare diseases, it is important to ensure that the ODA does not lead high prices that patients cannot afford. Some advice for improving the current ODA were proposed, but whether this will bring about the expected effects is unknown, such as if the price of orphan drugs will be lower without decreasing the number of newly marketed orphan drugs; fewer orphan drugs will be marketed at lower prices; or fewer orphan drugs will be marketed at higher prices.

In the following chapters, the simulation model of orphan drug innovation system is introduced to address the effectiveness and improvements of the ODA. Besides the ODA, the innovation process, the actors and their relationships in the system are the important components in the orphan drug innovation system. Hence, before introducing the computational model, the conceptual model of orphan drug innovation is introduced in the next chapter.

Chapter 4 Orphan Drug Innovation

From an idea to an approved drug in the market, orphan drug innovation comprises of four steps: discovery, designation, development and commercialization. Drug designation is unique to orphan drug. Drug discovery and development are complicated, expansive and time-consuming processes, which takes approximately 10-12 years and costs \$500 million to \$2 billion (DiMasi, Hansen et al. 2003). The incentives of the ODA ensure drug companies can recoup the R&D cost through drug commercialization.

With the significant advance of tools and technologies derived from biotechnology and genomics, in the recent decades, pharmaceutical research has evolved from a pattern where a random discovery dominated the drug discovery to a more rational and guided model. Through drug discovery, organizations typically find a drug candidate, which will progress to preclinical trial, and if successful, continue to clinical trials and finally become a marketed drug if the results of clinical testing meet the requirements of FDA approval. The FDA drug approval process includes pre-clinical studies testing the safety and effectiveness of the drug in animals and three phases of clinical trials. The drug companies with the marketing approval can sell the drug under market protection.

In this chapter, we will introduce the entire orphan drug innovation process from drug discovery, designation, and development to commercialization. Moreover, the main participants and their roles in orphan drug innovation, the relationship between participants, and the influence of science, technology and public intervention are also discussed in this chapter.

4.1 Orphan Drug Discovery

Translating an innovative drug from the original idea to a potential drug candidate is a complicated process. The origin of the idea comes from a variety of sources, such as academic and clinical research, or the commercial sector (Hughes, Rees et al. 2011). It takes many years to build up a collection of knowledge for starting a drug discovery process, and the new knowledge is developed through the whole drug discovery process. As Figure 16 shown, drug discovery process begins from initial target discovery and validation, hit identification, lead optimization to the selection of a candidate drug for the further clinical trials.

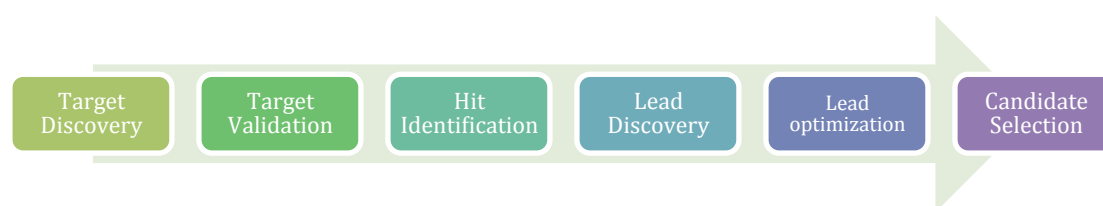


Figure 16 Drug Discovery Process

4.1.1 Drug Discovery Process

Drug discovery starts with a disease or clinical condition without appropriate treatment available, and there is underlying driving motivation for the discovery project. Most of the fundamental knowledge of drug discovery is from research organizations, which further develop that knowledge to hypotheses that the inhibition or activation of a protein or pathway will lead to a therapeutic effect in a disease state.

The outcome of the hypothesis is to discover a target, which can be proteins, genes, or RNA. The target is selected based on the understanding of the disease and the pathophysiological process that cause it. There are two types of targets: 'established targets' are those for which there is a good scientific understanding, based on some publications, and 'new targets' are those newly discovered

proteins or proteins whose function has now become clearer through basic scientific research.

Historically, drugs were discovered without knowledge about the disease. A large number of early discoveries in the pharmaceutical industry were through serendipity, where thousands of chemicals are applied to an assay that allows identification of compounds that produce the desired effect. Because drugs that are ineffective for the disease or unsafe do not qualify for FDA approval, drug identification is the critical stage in drug discovery process. Once a potential disease-causing target has been identified, a process of validation is carried out to examine the functions and effects of the target.

Target validation demonstrates that the target merits the development of drugs for the therapeutic application. This step is essential for researchers to prevent research paths that seem promising but finally lead to dead end. Validation techniques range from *in vitro* tools through the use of whole animal models to modulation of the desired target in disease patients (Hughes, Rees et al. 2011).

Following the target validation is the process of hit identification and lead discovery phase. Hit is a primary active compound with non-promiscuous binding behavior, exceeding a particular threshold value in a given assay; it needs to be resynthesized and confirmed to establish the validity of the hit (Keserű and Makara 2006).

Hits are progressed into a lead that can act on the target to change the disease course. There are several different ways to find a lead (Innovation.org 2007):

- **High-throughput Screening** This approach is the most common way to discover a lead. The rapid development of computation enables the researchers to test an enormous number of compounds against the target to find a lead with promising potential. Usually, several lead compounds are selected for further study.

- **Nature** Researchers turn to nature to discover interesting compounds for treating diseases. For instance, bacteria found in soil and moldy plants are found and developed into innovative medical products.
- **De novo** Due to advances in chemistry, researchers can generate molecules from scratch. They can use the complex computer modelling to simulate a molecule that may treat a specific disease.
- **Biotechnology** Researchers can genetically engineer a living system to produce disease-fighting biological molecules.

The final phase of drug discovery is lead optimization, which aims to maintain favorable properties in lead compounds while improving on deficiencies in the lead structure (Hughes, Rees et al. 2011). The objective of this step is to make the lead safer and more effective. By changing the structure of a compound, the lead can show different properties. For example, lead is modified to make it less likely to interact with other chemical pathways in the body, thus reducing the potential for side effects (Innovation.org 2007). During lead optimization, some variations of the leads are made and tested, and the best one becomes the candidate for drug development.

4.1.2 The Evolution of Drug Discovery

In the last century, pharmaceutical research has evolved from a pattern where a random discovery dominated the discovery phase to a more rational and guided process.

Random Drug Discovery

The traditional discovery of drugs is by ‘random screening’ through serendipity (Ratti and Trist 2001). The process is featured by high uncertainty because of

the lack of knowledge about the causes of diseases and the mechanisms of the action of drugs. A large number of chemical compounds are randomly screened in the lab to observe their effects. Finally, only a tiny proportion exhibits a promising potential. However, random screening was extremely successful during the period between 1950s and 1970s. A number of the significant discoveries, like the antibiotic Penicillin, resulted from a trial-and-error approach to optimization.

Rational Design

From the 1970s, the advances of biotechnology have improved the knowledge of disease mechanisms as well as the mechanisms of action of drugs. In turn, these advances opened up a new innovative door for drug discovery, from trial-and-error approaches to 'rational drug design' (Garavaglia, Malerba et al. 2010). Technology allows the design of a biopharmaceutical product based on natural products and the genetics of the disease. Biotechnology allows industrialized target detection and validation. As a result, biotechnology-derived therapeutics has been one of the most rapidly growing classes of new drugs.

Collaboration Network

Apart from the changes of drug discovery derived by technology, drug discovery process has hardly been successful by only one organization since the 1990s, especially for discovering an orphan drug. Many organizations are involved in this complex process, and they collaborate with each other to facilitate the knowledge transfer and decrease the risk.

A large number of biotechnology companies have emerged in this stage. Most of them are university spin-offs established by scientists with their latest research outcomes. This reflects a university commercialization process that begins with the formation of a company, which facilitates knowledge transfer from lab to industry. Many universities and institutions also provide university-backed venture funding and partnership with business expertise from business schools to encourage and promote the commercialization.

Especially, academic drug discovery is an ideal choice to tackle neglected and orphan diseases, because both have insufficient market size to recoup the cost of development. Drug discovery can be carried out using public funding and then the project can be passed on to drug companies for further development. Moreover, academic drug discovery provides a test bed for the development of new techniques of drug discovery and research in the practice of drug R&D. Although universities have played an essential role in drug discovery, they are not active in the subsequent process of translating these discoveries into marketable products. Most of the drug developments are invested by industry, and very few are supported by the public source. Besides, public organizations have played an important role in facilitating orphan drug R&D.

(1) PATIENT ADVOCACY GROUP

Different from the traditional model of drug research and development, advocacy groups are very important in increasing awareness and facilitating therapies for the rare disease patients. Firstly, they provide support for early-stage R&D, such as offering research funds and tools. Raising money and advocating for more public funding for rare disease research is one of the primary objectives of advocacy groups. Some disease-specific foundations have attracted researchers to take advantage of their knowledge and skills dedicated to a particular rare disease; while other funds have supported research training and career development to attract more investigators. Secondly, patient organizations have played an active role in drug development especially clinical trials. They maintain a close relationship with FDA and drug companies to organize members to participate clinical trials. These patient groups evolved a new kind of partnership with industry and public agencies to bridge the gap between basic research findings and approved products.

There are two main large patient advocacy groups in the US: National Organization for Rare Disease (NORD) and Genetic Alliance. NORD made significant efforts to prompt the enactment of Orphan Drug Act. Moreover,

NORD has offered about \$4.5 million to fund 110 grants and fellowship (WÄStfelt, Fadeel et al. 2006). Genetic Alliance is a coalition of over 600 patient groups and represents the interests of patients with genetic diseases to increase the awareness of the rare disease in government and Congress.

(2) NIH

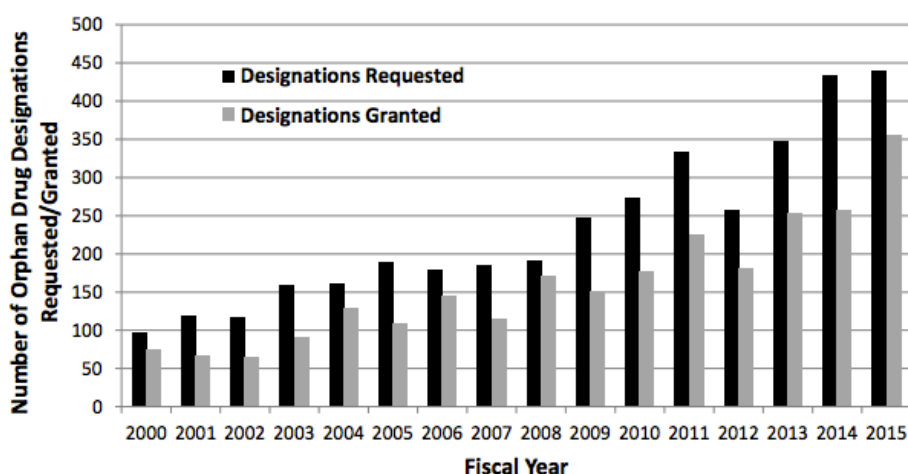
Since the industry funds relatively little basic research, publicly funded basic research is the basis for orphan drug development. The main funding source for basic research on rare disease is from NIH. The number of NIH funds granted for different rare diseases varies from zero for tetralogy of Fallot and one for Ehlers-Danlos syndrome to over 600 awards for Huntington's disease and approximately 800 awards for cystic fibrosis. It indicates that some rare diseases have received substantial funding, while some rare diseases have not attracted any funding at all. The variation can be attributed to two factors: firstly, the gene mutation of some rare diseases has been identified, which attracted a number of NIH funding; secondly, robust and high-profile patient-specific advocacy groups can garner funding from NIH for those diseases.

4.2 Orphan Drug Designation

Once a drug with a potential therapeutic effect has been found, a company or a researcher applies to the FDA's Office of Orphan Products Development (OOPD) for its orphan drug designation. OOPD will review the documents systematically and decide whether it is eligible for orphan designation. The eligibility of designation application is 1) a previously unapproved drug or 2) a new orphan indication for an approved drug or 3) the 'same drug' as one already approved but with a potential to be 'clinically superior.'

It is expected that OOPD could make a decision in less than 90 days, and roughly 60%-70% of applications result in granting orphan status. Figure 17 shows that between 2000 and 2010, 353 of the 2,278 orphan designations issued by OOPD

obtained marketing approval. Moreover, the number of requests for orphan designations and the number of granted orphan designations have both doubled in the last ten years.



(Source: (OOPD 2016))

Figure 17 The Requested and Granted Orphan Drug Designations

According to the FDA database for Orphan Designated and or Approved Products, until the end of 2015, there are 3500 orphan designations issued by OOPD, with over 500 of them having resulted in marketing approval with orphan exclusivity. During the FY 2015, OOPA reviewed 440 Orphan Drug designation applications; the number of applications for orphan designation has quadrupled since FY 2000. In FY 2015, 76.1% (335) of the applications were approved by OOPD, and 40 orphan designated drugs were approved for marketing, which accounts for 33% of the new molecular entities that the FDA approved.

Table 11 Orphan Drug Designation and Market Approvals from FY2008 to FY2015

	FY 2008 Actual	FY 2009 Actual	FY 2010 Actual	FY 2011 Actual	FY 2012 Actual	FY 2013 Actual	FY 2014 Actual	FY 2015 Actual
Designation Requests	192	248	273	334	259	330	434	440
Designations Granted	164	152	177	225	179	235	285	335
Market Approvals	10	19	11	25	20	36	45	40

Obtaining orphan status for a drug under development enables the sponsor to get benefits from the formal incentives of the Orphan Drug Act like tax credits for clinical development and seven years of exclusive marketing after FDA approval, as well as informal incentives such as development assistance from the Orphan Products Office and funds from venture capital or other sources.

The orphan drug designation was considered as a surrogate for the company to develop a drug for a rare disease. But, not all the drug developers might seek drug designation through FDA due to the patent consideration, and the information about their drug development may not be easy to access. Moreover, the time from designation to approval may not be the real drug development time, as the orphan designation may be applied at any time of drug development. The median time from designation to approval is 2.49 years (interquartile range 1.13–4.64) for rare cancer (Stockklauser, Lampert et al. 2016); the mean time for RRDSs (Rheumatologic Diseases) is 3.9 years (Ries, Lutz et al. 2015); and the mean time for Gaucher disease is 4 years (Mechler, Mountford et al. 2015).

Orphan drug designation is of special value for the drugs that are questionable whether they would apply for orphan drug status (FDA 2010). The orphan drug designation status allows the sponsors of drugs and biologics to enjoy the ODA incentives including tax credits and market exclusivity. The approval of orphan designation does not change the standard regulatory requirements or process for marketing approval, and the safety and efficacy of a drug should still be evaluated based on adequate and well-controlled studies.

4.3 Orphan Drug Development

Orphan drug development involves the same processes as any other drugs and aims to demonstrate the effectiveness and safety.

4.3.1 The Stage of Drug Development

To assess the efficacy and safety of a drug, the FDA drug approval process consists of pre-clinical studies that test the safety and efficacy of the drug in animals and three phases of clinical trials in humans. The process of clinical trial is stepwise, with each step building on the results of previous studies. Clinical experiments can be categorized into three phases of testing. Phase I clinical trial collects data about the safety of the drug in humans through a small group of healthy volunteers (20-100). Phase II assesses how the drug works and establishes the short-term single-dose efficacy through larger groups of patients (20-300). To establish both the short-term and long-term efficacy, Phase III trials are conducted on a larger patient cohort (300-3000 or more).

The path a drug does through from a lab to the market is long and complicated, and every drug may take a unique route. Most drugs undergo eight steps of testing in animals and humans and then get reviewed by the FDA (Figure 18).



Figure 18 The Step of Drug Development

4.3.2 The Flexibility of Orphan Drug Development

Since a rare disease is defined as “any disease or condition that affects less than 200,000 persons in the United States”, the patient population available for testing orphan drugs is much smaller than non-orphan drugs for more prevalent diseases. In addition, the number of patients with specific rare diseases can vary, and some rare diseases affect thousands of patients while some affect only a handful of patients. For example, NAGS deficiency affects

fewer than ten patients in the US while Gaucher disease affects approximately 2000 persons in the US (Goodman 2010). Based on these characteristics of the rare disease, FDA provides flexibility for the evaluation of safety and efficacy of orphan drugs.

As cited by Dr. Goodman, FDA Chief Scientist and Deputy Commissioner for Science and Public Health, in the testimony to the United States Senate:

- NAGS deficiency, the rarest of the Urea Cycle Disorders (UCDs), affects ten patients in the US. Carbaglu (Carglumic Acid) was approved in March 2012 based on data derived from fewer than 20 patients in comparison to a historical control group.
- VPRIV for the treatment of Gaucher disease affecting about 2,000 persons in the US, approved in February 2010 based on a clinical trial of 100 patients and a pivotal study with 25 patients.
- Myozyme for the treatment of infantile variant and rapidly fatal form of Gaucher disease was approved in April 2006 based on a drug development program of fewer than 80 patients and a pivotal study of 18 patients.
- Ceprotin, human plasma-derived protein C concentrate, is used to treat severe congenital Protein C deficiency. Less than 20 patients were known in the US. This biologic drug was authorized marketing approval in March 2007 based on a clinical trial of 18 patients using the comparison to historical control data.

As the above cases such as Ceprotin and VPRIV show, for some orphan drugs, the smaller number of patients enrolled in the development result in faster drug development and lower development costs.

The same as other diseases, FDA is fully committed to the development and review of products for rare disease (Goodman 2010). FDA grants an approval for a new drug based on substantial evidence of effectiveness derived from adequate and well-controlled investigations. The evidence for effectiveness should satisfy the requirements, which are referred to as 'two adequate and

well-controlled studies'. However, 'two adequate and well-controlled studies' are not easy to achieve in orphan drug development. Alternatively, the design of a clinical trial for evaluating an experimental treatment for a rare disease may follow special approaches (Griggs, Batshaw et al. 2009).

During the previous decades, the FDA has introduced two ways of providing flexibility for reviewing new drug applications. Although neither of them is designed for orphan drugs, they are widely used for orphan drug approval (Sasinowski 2011). The first policy is to review the application based on a single adequate and well-controlled trial for nine different circumstances. Usually, the FDA needs at least two adequate and well-controlled studies. Within this guidance, FDA can approve a drug when one single study is sufficient under specific circumstances. The second one is 'fast approval' used to review the serious disease with unmet medical need, such as AIDS and some cancers. The evidence of fast approval should be based either on an invalidated surrogate that is reasonably likely to predict ultimate clinical outcome or on a result other than irreversible morbidity or mortality. FDA created these programs to bring the medical products to markets as early as possible to meet the needs of patients with serious disease and unmet medical needs.

In NORD's study, two thirds of approved orphan drugs employed flexibility into their evaluation. 32 of 135 orphan drugs analyzed manifests administrative flexibility and another 58 orphan drugs were approved on a case-by-case application of flexibility. The flexibility of orphan drug review reinforces the need for the public acknowledgment that orphan drugs need special considerations. In many cases, it is not possible to conduct randomized, double-blinded, placebo-controlled studies with orphan drugs, and alternative personalized study designs are often required (WÄStfelt, Fadeel et al. 2006). Designing the clinical trial is another critical problem for sponsors.

Some of the successful examples summarized by Dr. Goodman are as following:

- Amifostine under the trade name Ethyol was approved in 1995, and it is used to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer. The review of Ethyol illustrates the later FDA 1998 guidance about ‘single study’, which means one study has a statistically very persuasive finding and another study is likely unethical.
- Rilonacept, of which the trade name is Arcalyst, is used to treat some of the symptoms of rare genetic condition Cryopyrin-Associated Periodic Syndrome (CAPS). The 2008 approval is based on a single double-blinded placebo-controlled study, due to the rarity of this condition, FDA allowed two segmented parts of study with separate randomizations for each part, Part A (n=47) and B (n=45). Both parts of the clinical trial met their primary endpoints, and because the drug was designated as a Fast Track drug, it received a full approval without a confirmatory Phase IV study.
- Thalidomide, the trade name is Thalomid, was approved in July 1998 for treating erythema nodosum leprosum (ENL). The approval of Thalomid was based on primary data that demonstrates the efficacy of thalidomide from the published medical literature and a retrospective study of 102 patients treated by the US Public Health Service (PHS). The statistical data from long-term medical records is not from an adequate and well-controlled study.
- Sterile Talc Powder, with the trade name Sclerosol, was approved in December 1997 for treating malignant pleural effusions based only on published literature. The statistical review of Sclerosol notes that: “Talc has been used for years to treat patients with malignant pleural effusions, but talc has never been approved by the FDA for this purpose.” In judging that substantial evidence of efficacy was sufficient, five of the published studies were reviewed by the FDA as being of more reliable design and/or quality. Only one of five showed a statistically significant higher response rate in the trial group than in the control group.

From the above examples, it is not hard to find that research resources of rare diseases are limited, and the most precious resource is the patients with rare diseases who are willing to participate in clinical trials; most of the clinical trials are conducted with less information than the tests of drugs for other conditions about the safety and efficacy of the investigational therapy from animal models and human trials.

Different parties may have different opinions on the trial design and the interpretation of the results. The FDA has made its scientific judgment to interpret and apply the standards in a flexible manner, based on the circumstances of each therapy for each rare disease. However, no clear formal policy expressing the flexibility is provided in FDA's application of the statutory standards of safety and efficacy for orphan drugs. NORD appreciates FDA's efforts on flexibly reviewing applications for orphan drugs, but it requested FDA to issue a policy on how to exercise flexibility in a systematic way into its review of therapies for rare diseases (Sasinowski 2011).

4.3.3 The Platform of Cooperation for Orphan Drug Development

The clinical trials for drugs treating rare diseases are subject to the same requirements for efficacy and safety as other drugs. Although orphan drug development can take advantage of flexibility the FDA provided, it faces severe challenges and difficulties that are not usually encountered in the clinical trial for prevalent diseases. Obviously, the biggest challenge is the small number of trial population and the patients are often geographically dispersed (WÄStfelt, Fadeel et al. 2006). How to design the clinical trials with such a small number of populations and judge the results from the limited trials are the main obstacles for orphan drug development.

Most of the sponsors applying orphan drug designation are small biotechnology companies, which lack patients and regulatory and clinical trial experience (WÄStfelt, Fadeel et al. 2006). To ensure sufficient patients are enrolled in the

investigation and the design of the clinical trial is robust, coordination is necessary for the orphan drug development.

RDCRN

RDCRN (Rare Disease Clinical Research Network) is a patient contact registry sponsored by NIH. This organization collects data, such as patient contact information, diagnosis, and medical history, with the aim of providing information to drug companies and research organizations about a specific rare disease.

RDCRN provides assistance for drug development as it maintains the close relationship with patients. The RDCRN has supported the rare disease R&D in the following ways:

- 1) Support the collaboration in clinical research, including longitudinal studies, clinical studies, and clinical trials.
- 2) Train clinical investigators for rare disease R&D
- 3) Assist in proof-concept clinical trial projects
- 4) Facilitate information flow among researchers, physicians, patients, healthcare officers, and the public.

FDA

The FDA organizes a series of workshops to discuss important and difficult research on orphan drug discovery and development. FDA also strengthens the network to increase transparency, share advice and establish new programs with several patient organizations, including NORD, ORDR, TRND, the National Institute of Neurological Disorders and Stroke (NINDS), patient advocacy groups, academia and the Institute of Medicine (Goodman 2010).

With the responsibility to assure the safety and efficacy of orphan drugs, the FDA is fully committed to applying the requisite flexibility in the development and review of products for rare diseases. A lot of the approved orphan drugs

have been examined on a limited number of patients, serving as the evidence of FDA's commitment to these patients.

In 2010, two expert working groups, Rare Disease Review Group and Neglected Disease Review Group, were established by FDA. These two internal review groups are aiming to address the rare and neglected disease and report to Congress one year after establishing the groups to issue guidance relating to rare and neglected disease.

- **Rare Disease Repurposing Database**

The existing drugs are proven to be safe in patients, therefore if they are found to be effective for other diseases, repositioning these drugs would dramatically reduce the drug development time, costs and risks (Kollewe 2012). In 2010, OOPD announced a new tool called Rare Disease Repurposing Database, which provides data about drugs already approved by FDA for another disease and are deemed with potential for treating rare disease nowadays. According to FDA RDRD (Rare Disease Repurposing Database), until 2010, there were 168 orphan-designated drugs with at least one marketing approval for a common disease indication, 183 orphan-designated drugs with at least one marketing approval for a rare disease indication, and 105 orphan-designated drugs with at least one marketing approval for both common and rare disease indication (RDRD 2012). The feature of this database is to shorten the duration and decrease the cost of the repurposing drug so as to bring great benefits to the patients.

- **Regulatory Science**

Researchers have defined the genetic basis of over 2,000 rare diseases and discovered potential drug targets for many rare conditions, but, there exists a large gap between the outcomes of basic science and applied product development (Goodman 2010). FDA regulatory science research intends to bridge this gap and accelerate the transformation of research into medical products to introduce more safe and effective products to the public. The

regulatory science is the tools, methods, assays, standards, and models that help facilitate the drug development, review and approval. The FDA provides funding to strengthen the scientific infrastructure and capacity to leverage the opportunities to enhance the scientific collaborations. FDA helps drug companies to improve the drug development process through providing new and emerging technologies, modernizing the standards for evaluating products and speeding up the development process of novel medical products.

OOPD administers the majority incentives of the ODA of 1983 which stimulate drug companies to develop products for the patient population that otherwise would be considered too small to develop and market medical products for them. With the aim to assist and stimulate the identification, development, and availability of both safe and effective products for patients with rare diseases, the FDA Office of Orphan Products Development (OOPD) has three primary missions: the first mission is conducting scientific and regulatory review of orphan drug designation; secondly, OOPD awards and manages grants to defray orphan products clinical study costs; and the third is serving as a liaison for drug companies, FDA review divisions, patient advocacy groups and other government agencies (Needleman 2012). It also plays an essential role in providing expertise in clinical trial design and outcome review, helping sponsors resolving any outstanding problem in the drug development process.

Advocacy Group

Patient advocacy group plays a significant role not only in the introduction of the ODA in the US, but in the supporting orphan drug development. Patient advocacy group facilitates the drug development process by helping with patient recruitment, research funding, administration of patient assistance programs and improving the communication between patients and doctors (Griggs, Batshaw et al. 2009). The largest advocacy group in the United States is National Organization for Rare Disease (NORD). NORD provides assistance with patient recruitment, and it shares the information about opportunities to participate in clinical trials and give the necessary travel and temporary housing

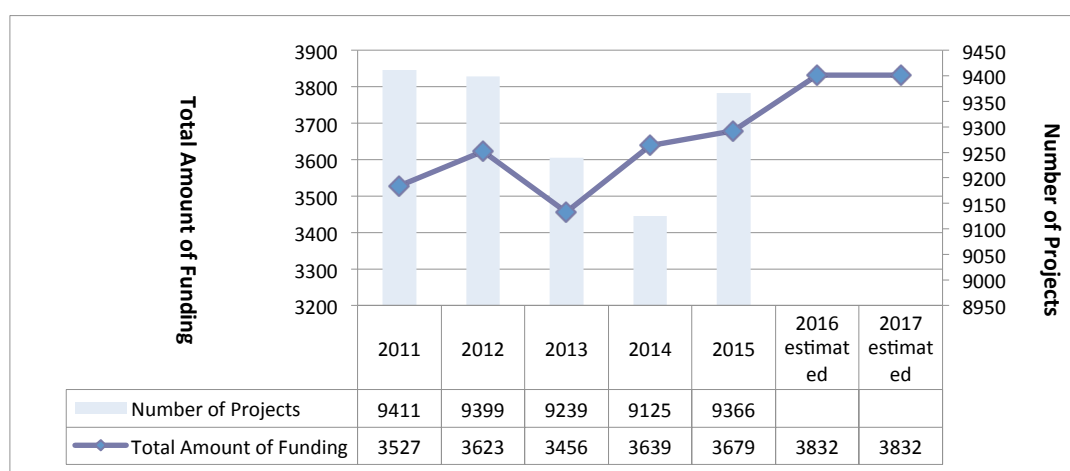
assistance for the patients and their families who have to travel to a distant place to participate in clinical trials.

The efforts of different organizations work together to help to make the promising drugs for rare diseases from concept to products more quickly and efficiently.

4.3.4 Funding Orphan Drug R&D

4.3.4.1 NIH

The Office of Rare Disease Research (ORDR) was established in 1993 within NIH, and it became a centralized dataset on rare disease clinical research and a communication media among patient groups, research, and government. The NIH funding for rare disease research is \$3679 million, and this amount will increase in 2016 and 2017 (Figure 19).



(Data Source: (NIH 2016))

Figure 19 NIH Funding for Rare Disease from 2011 to 2017

Rare Diseases Clinical Research Consortia (RDCRC)

The ORDR started a second phase re-competition for funding support for the Rare Diseases Clinical Research Network (RDCRN) and Data Management and Coordinating Center (DMCC) in 2009.

RDCRN firstly established in 2003 by Office of Rare Disease (ORDR), works closely with patient groups and research organizations to support the rare disease R&D. The Contact Registry in RDCRN links the registered patients to RDCRN, and the patients would be contacted when there are clinical research opportunities and informed about the progress of research projects. RDCRN has 22 Rare Diseases Clinical Research Consortia (RDCRC). DMCC supports the consortia through providing technologies and tools to collect and analyze clinical research data.

Each consortium supports the clinical protocols for a minimum set of three related rare diseases with guidance from one or several of participating institutions. The rare diseases have been funded for five years include Autonomic Disorders Consortium, Urea Cycle Disorders Consortium, Lysosomal Disease Network, Clinical Investigation of Neurologic Channelopathies, etc. The RDCRC on Urea Cycle Disorders (UCD) has been funded by NIH since 2003, consists of 15 sites in the US and two international sites, and involves over 50 investigators and staff. The main duty is to carry on a longitudinal natural history study investigating morbidity, mortality, and biomarkers in over 500 adults and children with UCD in the US, Canada, and Europe; supporting the Phase II trials of new drugs, and assessing neural mechanisms of injury by innovative neuroimaging and neuropsychological testing procedures.

Between 2009 and the end of September 2013, 18000 participants had been enrolled in 84 multi-site clinical research studies; 151 clinical researchers have been trained in the rare diseases research; 24 studies had finished the recruitment and were in the final analysis phase (NIH 2016). Most of the funded organizations are the universities, such as the University of Pennsylvania, the University of California, Columbia University Medical Center, and the University of North Florida.

In 2014, the entire rare disease research program was relocated under the auspices of National Centre for Advancing Translational Sciences (NCATS),

which is the new home for NIH ORDR. It has 22 funded consortia to study on over 200 rare diseases in cooperation with 98 advocacy groups. The network will become more productive in the future. It has generated a large number of research outcomes including books, conference proceedings, conference papers and journal articles.

4.3.4.2 Research Grant Program by NORD

NORD support to industry for both research and development of orphan drugs and provide grants and fellowships for the studies of rare disease. A lot of patient advocacy groups have developed sophisticated and highly effective strategies to support the research of rare disease (Griggs, Batshaw et al. 2009). The Research Grant Program is funded by patients and patient organizations, from which the donations are targeted at specific disorder. It is the only source of funding for studying certain rare diseases. The minimum amount needed to fund a grant is \$35,000. Once the minimum amount is reached, NORD will start the process of issuing a research proposal; if the donated funds for research is less than the target, the fund will be transferred to research on the specific disease (NORD 2016).

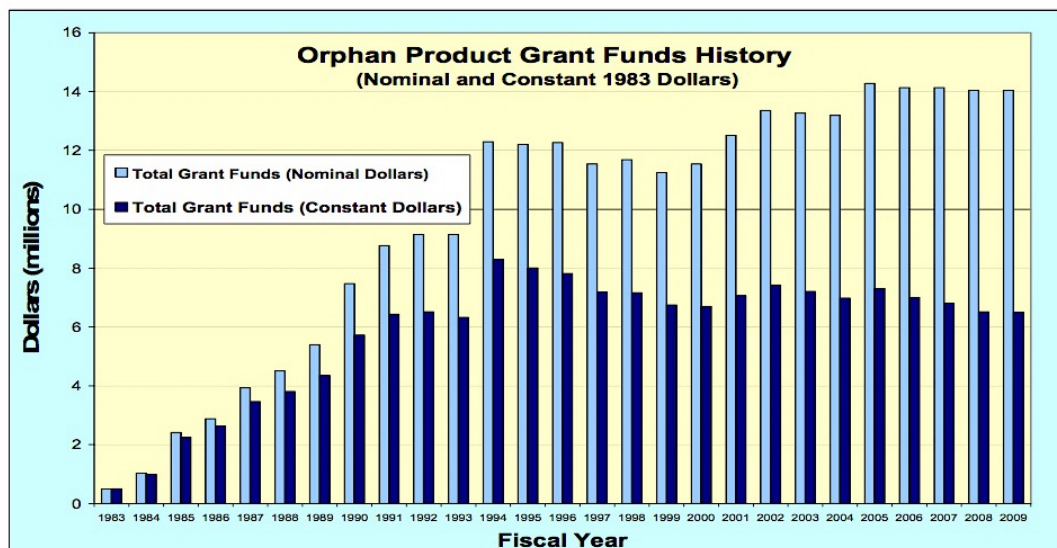
4.3.4.3 Orphan drug Grants Program

The objective of orphan product development grant program is to stimulate the clinical development of products for the treatment of rare diseases and conditions through helping sponsors in defraying the costs of clinical trials. Since 1983, the OOPD has provided over \$350 million to fund more than 7000 clinical studies and supporting more than 55 products to get the marketing approval. Orphan Drug Grant Program only supports the clinical studies: phase 1 studies are qualified for up to \$250,000 per year for less than 3 years, Phase 2 and 3 studies are qualified for up to \$500,000 per year for less than 4 years.

This program has funded about 10% of all orphan drug approvals, and the current annual budget is approximately \$14-15 million (OOPD 2016).

- The program is open to any foreign or domestic, public or private, for-profit or nonprofit entity including state and local units of government.
- The products are required to be the drugs, biologics, medical devices and foods for medical purposes that are indicated for rare diseases.
- Both the drugs with and without orphan drug designation are eligible for the grant program.

With the increase of drug development costs, OOPD grants are covering less and less of the cost of drug development, but the speed has slowed down since 1995 (Figure 20). According to the constant dollar value, the amount of grant in the 21st century is a little less than in the late 1990s.



(Source: (OOPD 2012))

Figure 20 The Orphan Product Grant History from 1983 to 2009

The total amount of OOPD funding, which includes Orphan Product Grants, Pediatric Consortia Grants and program administration, has increased steadily since 2016. But, orphan product grant doesn't grow as fast as OOPD funding (Figure 21). In FY 2015, 18 new grant awards were offered-out of 92 applications, and OOPD kept supporting about 67 other ongoing clinical studies (OOPD 2016).

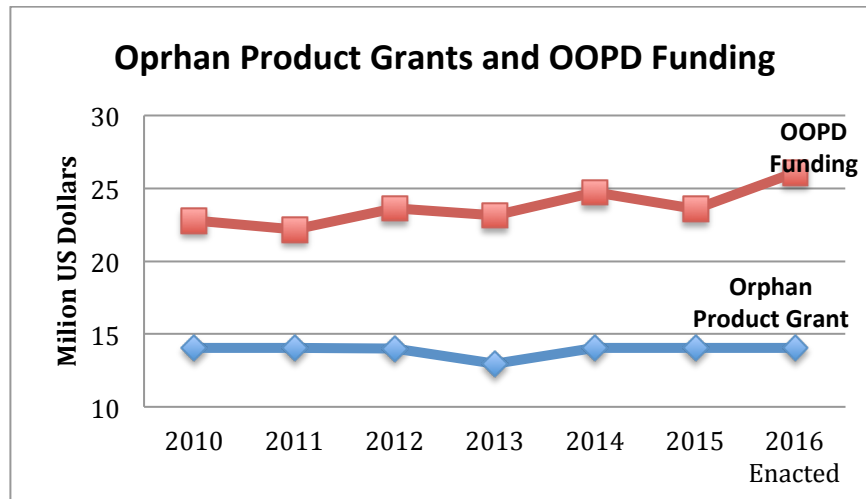


Figure 21 The History of Orphan Product Grants and OOPD Funding from 2010 to 2016

Nearly half of the grants have been awarded to research organizations. For instance, in FY 2012, 13 of the 17 new grants were awarded to research organizations such as University of California San Diego, University of Pennsylvania and Massachusetts General Hospital; three were awarded to biotechnology companies including Apogee Biotechnology Corporation, Spineform LLC, and Tolera Therapeutics Inc.; one was granted to non-profit medical care organization, Mayo Clinic. 23% of the grants were used to support Phase I clinical study, while 66% grants were used to support Phase II clinical study, 4% to fund Phase I and II clinical studies and 7% for Phase III clinical studies (Figure 22).

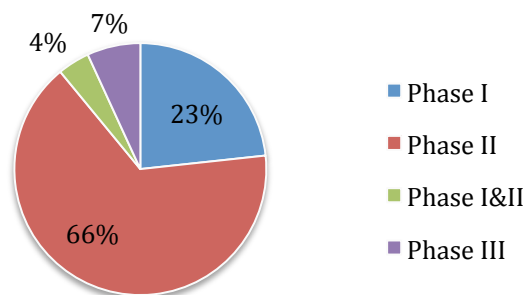


Figure 22 The Distribution of OOPD Grants from 2011 to 2015

OOPD grants make the drug development occur in a timely manner with a very modest investment. Not only products approved with the support of OOPD grants, but a big number of publications have also resulted from OOPD grants funded research that has improved the health of patients with rare diseases in the US.

4.3.4.4 Orphan Products Natural History Grants

At the beginning of 2016 FDA announced the availability of \$2 million grants to support research on the natural history of rare diseases. The objective of this project is to “help characterize the natural history of rare diseases, identify subpopulations, and develop and/or validate clinical outcome measures, biomarkers and companion diagnostics (OOPD 2016)”. It is the first time that FDA offers funding through Orphan Product Grants to support these types of research. Rare diseases are usually poorly understood, without the understanding of how rare disease progress it's hard to develop the medical treatments. The knowledge about natural history of rare diseases will help to design clinical trials, identify endpoints, and further contribute to fast tests and effective products. In FY 2017, 2-4 grants will be offered to support the natural history studies of the rare disease (OOPD 2016).

4.3.5 The Accelerated Orphan Drug Development Process

From pre-clinical trial to final review, the drug development process is a long and complex journey for sponsors. A lot of trials have to be organized and completed, a vast number of data have to be analyzed, many documents have to be filed and submitted to FDA, various parties have to be negotiated and some difficulties in designing trial have to be overcome. FDA uses a variety of tools to speed up the orphan drug development, these tools including Fast Track, Priority Review, and Accelerated Approval. All these programs address a broad range of serious disease including rare diseases.

Fast Track

Fast track, which was developed by FDA, a process designed to facilitate the development and shorten the review of drugs to treat serious diseases and meet unmet medical demands. The aim is to ensure the important new drug to the patient earlier.

Determining whether a drug is eligible for Fast Track is based on: 1) the drug is developed to treat a severe disease, some of the examples are AIDS, heart failure, and cancer; 2) filling an unmet medical need is defined as providing therapy which does not exist in the market or is superior to existing therapies. Most of the orphan drug meet one of the above requirements and qualifies the Fast Track. Once a drug receives Fast Track designation, drug companies will meet more frequently with FDA to discuss the plan of drug development and receive more frequent feedbacks from FDA about the design of clinical trials. Drug companies are encouraged to meet with the FDA early and frequently throughout the whole process of drug development and review. The frequency and early communication makes the questions and problems be resolved quickly and makes the risk of drug development lower. Therefore, Fast Track leads to earlier drug approval and access by patients.

Priority Review

In 1992, the FDA established a two-tiered system of review times, including Standard Review and Priority Review. Standard Review is applied to a drug that offers a minor improvement over existing marketed drugs; the goal of review time is ten months. Priority Review is designed for drugs that provide a treatment where no adequate therapy exists or significant advances in existing treatment.

Both drugs treating serious diseases and less serious diseases are eligible to apply for Priority Review. The objective of finishing Priority Review is six months. Most drugs receiving Fast Track designation are likely to be considered appropriate to be eligible for Priority Review (FDA 2012). For example, JAKAFI

and ERWINAZE approved in 2012 was designated as Fast Track and reviewed under the six-month Priority Review program.

In the FY 2012, nearly half of the marketed orphan drugs were approved under Priority Review program (Table 12). The study shows that, during the decade from 1993 to 2003, the median review time of priority is approximately half of the review time of Standard Review (FDA 2012).

Table 12 The New Marketed Orphan Drugs in FY 2012

Drug Name	Approval Date	Priority Drugs	Standard Drugs
ERWINAZE	11/18/11	✓	
JAKAFI	11/16/11	✓	
KALYDECO	11/31/11	✓	
VORAXAZE	01/17/12	✓	
BOSULIF	09/04/12		✓
ELELYSO	05/01/12		✓
FERRIPROX	10/14/11		✓
KYPROLIS	07/20/12		✓
ONFI	10/21/11		✓

(Data Source: (OOPD 2012))

Accelerated Approval

Accelerated Approval was instituted in 1992 to make the drugs treating serious disease and filling an unmet medical need. The method used to stimulate the approval is based on the surrogate endpoint that is a measurement in the laboratory or physical sign applied in clinical trials as an indirect or substitute measurement that indicates a clinically meaningful outcome. That means the approval of a drug is based on the clinical results rather than learning whether patients benefit from the drug.

The application of surrogate endpoint in drug development can save valuable time. The research on the approved drugs between 2000 and 2005 shows that

accelerated approval products were approved 4.7 months faster than non-accelerated products (Faden and Kaitin 2008). Phase 4 trials are required to confirm the expected clinical benefits if the confirmatory trial shows that the drug has the clinical benefits then the FDA offers approval for the drug, once the trial does not show the drug has the expected clinical benefits, the FDA removes the drug from the market according to regulatory procedures.

Based on 20 orphan drugs approved between 2000 and 2005, the mean approval duration for products approved by FDA was 15.5 months (Faden and Kaitin 2008). This can be considered as resulting from the effect of regulations enacted by FDA to facilitate drug review process. In all, Fast Track, Priority Review and Accelerated Approval combined with flexible clinical development are methods that are designed to make orphan drugs available at an earlier time, but they do not alter the scientific or medical standards for approval or the necessary quality of evidence.

In summary, the development of orphan drug typically takes less time than non-orphan medications (Bohrer and Prince 1998). Firstly, this may be because the orphan drug application usually has a smaller number of patients and fewer clinical trials. Secondly, a more significant proportion of orphan drugs were benefited from priority review and accelerated review procedures, which was designed to accelerate the development and approval of drugs and biological products treating unmet serious or life-threatening diseases. Thirdly, OOPD works closely with medical and research communities, professional organizations, academia, drug companies and patient organizations. These close relationships facilitate the enrolment of volunteers and patients in clinical trials for orphan products, even though the number of patients is small, and patients are geographically dispersed.

4.4 Orphan Drug Commercialization

Before Orphan Drug Act, drug companies rely on the patent to protect the technology and market of their products. Drug companies typically apply for a patent, because patent protection precludes other companies from applying for a patent on the same drug and selling it. The small companies, for instance, the start-up biotechnology companies, rely heavily on patent protection to secure the investment on R&D. However, a number of the orphan drugs are not patentable, and some drug has already been patented, so the market exclusivity is of significant value for these drug companies. The market exclusivity makes the small orphan drug market with big potential. There are three main issues concerning the orphan drug commercialization.

4.4.1 The Cost of Orphan Drug Discovery and Development

The cost of discovery and development of a new drug was estimated to exceed \$1.3 billion in 2006 (DiMasi and Grabowski 2007). The cost structure of the pharmaceutical industry is much different from other sectors. Firstly, drug R&D involves a large number of sunk costs; companies have a very high upfront cost of R&D and commercialization cost, and sunk costs that stem from the high rate of failure. Second, the marginal cost (manufacture) of drugs is relatively low. Third, a high return should be achieved to offset the high cost of R&D.

Drug companies can benefit from the FDA funding program to reduce the drug development cost, such as application, product and establishment fee waiver, tax credit enabling drug company a 50% off of the cost for human clinical trials, grants supporting clinical trials. All these programs help the sponsors save considerable money during drug development process.

The cost of orphan drug development is not as considerable as non-orphans, for instance, the cost of developing an HIV/AIDS drug is around \$479 million while

the rheumatoid arthritis drug's development cost is nearly double of HIV/AIDS's (Adams and Brantner 2006).

4.4.2 The Market of Orphan Drug

Because of the high cost of R&D and the small probability of success for each drug candidate, drug companies should work extensively on the marketing to ensure their share in the competitive market. Whether the approved drug delivers considerable returns and profits to the company depends on the ability to set a reasonable price and sufficient sales volume over the period of market protection. In the orphan drug market, the active networked relationships among patients, advocacy groups, and medical expertise make the market penetration faster than non-orphan drugs (Milne 2002). Therefore, there is less need for advertising and considerable sales effort to prompt the orphan drugs.

4.4.3 Price an Orphan Drug

Medicines are considered as a necessity for the public, and the change in price will drive some people out of the market. The pricing of medicine is entirely different from pricing other products; firms control the price to make sure that the public takes the expected quantities at that price (Reekie 1977). Setting a reasonable but adequate price for a new product is crucial for the drug company. If the price is set too low, the return on investment is not sufficient to recoup the R&D cost and support the continuing business; if the price is set too high, customers may choose not to use this product, resulting in the same problems for the company.

The price paid for a medicine comprises a number of components. Along the supply chain from manufacturer to patient, various components are cumulatively added into the manufacturer's selling price (MSP), such as freight costs, taxes, markup, and procurement fee. The sum of these fees isn't low,

accounting for 30%-45% of the dispensed medicine price on average, and it can be much higher. In our model, drug pricing refers to the manufacturer set the price for a drug.

Factors influencing drug pricing

In the pharmaceutical industry, pricing a medicine is increasingly important, because drug companies need to ensure that they can achieve a high return in order to recoup the costs and gain sufficient profits. Setting an optimal price for the new product can lead to the market success and maximize the profit of the drug company. In the following sections, we describe the methodological framework that is used by many drug companies to set the price, the factors influencing the pricing are explored, and the strategies of setting and adjusting the price are discussed.

Pharmaceutical industry features a low ratio of variable or direct cost to total costs. Variable costs refer to the cost of production, distribution, and promotion, while the pharmaceutical research and development costs are substantial and fixed. Therefore it is impossible for companies to set the price at the marginal costs in the pharmaceutical sector.

The mechanism of drug pricing is very complicated. For most researchers, the process is like a black box, as they know little about the details of how companies price a drug. Pricing strategy employed by drug company varies widely according to a number of factors, including the perceived therapeutic value of the drug, the degree of novelty that the drug compared to the existing products, the degree of product substitution, the investment costs of drug research and development, the costs of manufacture, promotional expenditure, the duration of patent protection, the price of competitive prices for alternative therapies, potential new competitors, and government intervention.

There are four main models widely used for drug pricing:

1. Cost-based pricing (CBP): The price of the medicine is set at the sum of the cost plus a constant margin to make profits. This model is a product-driven model, it does not take into consideration supply and demand or even the market positioning.
2. Value-Based Pricing (VBP): This model is based on the pharmacoeconomics. It is an efficient model for determining the price of medicine according to the economic value. The principle of VBP model is based on the benefit the product can offer to its customer and maximize the return through a structured evaluation of products cost and outcomes. The value-based pricing model is able to help create the true benefits to the society; it has been highlighted by many experts and governments. It offers the best value for money spent, but it's tough to evaluate and quantify the value of the drug's outcome.
3. Target return pricing (TRP): This model of pricing firstly estimates the drug company's desired return on the investment and then add them in the price of the drug. The objective of this strategy is to achieve target return-on-investment.
4. Reference pricing: In this model, the price of the drug is determined according to its competitors' price in the market. The reference drug is another drug in the same therapeutic class, and it may be the drug with the same clinical indications or the drug not available in the country where it launches. This strategy is widely used in the countries with government intervenes pharmaceutical price, like Germany, Netherlands, Spain, and the UK, it has driven down pharmaceutical prices in these countries. The reference pricing model can be considered as a price control mechanism in the pharmaceutical market, both the government and patient save money in the reference-pricing mechanism. Patients are free to choose different drugs in the same therapeutic category, and they

should pay the difference between the cost for reimbursement purpose if they want a more expensive drug.

All the strategies above have their advantages and shortcomings, and drug companies usually integrate some of them to set the price for a new product. The prices of the same drug may differ among different countries. Different healthcare systems between the US and Europe result in different pricing environments: free-pricing and price-controlled market. In Europe, countries impose strict government control over drug price, while the US healthcare model has led to a free market for pricing. Drug price is controlled by the market forces in the US, and drug company can determine the price for its products and adjust the price over time in terms of inflation and market situation.

For the orphan drug pricing in the US, the process of setting the price for a new product starts from the early stage of drug development, usually many years before the launch. The drug company estimates the value of the drug to its consumers and the desire and ability of its consumers to pay for it (VBP). Moreover, the company determines a price threshold over which the cost of R&D investment will be sufficiently covered, and a good return is obtained (TRP). Therefore, orphan drug pricing includes the strategy of VBP and TRP; in addition, the market monopoly period is of significance in pricing a drug. During market protection period, the drug company is the only firm in the sector producing the medical product; no completion makes the company charge a monopoly price that will be above the firm's marginal cost.

4.4.4 The Revenue Flow

The revenue flow of orphan drugs is distinct from non-orphan drugs (Milne 2002). The revenues of typical mainstream drugs increase rapidly after launch, peak after 11–12 years then decline quickly. The revenue curve of an orphan drug is smoother with slower growth and decline than other drugs, and the

peak sales period is 15 years after launch (Grabowski and Vernon 2000). Because of less competition, drug companies can still maintain the high revenue even after 7-year market protection.

4.5 Summary

Orphan drug innovation is a long and expensive process, and it's influenced by a variety of factors. The rapid development of science and technology altered the traditional drug discovery process from random screening to rational design and to the research featured by network collaboration; the regulations like flexibility of drug development, Fast Track, Priority Review and Accelerated Approval shorten the drug development process for drugs treating severe and unmet diseases; the orphan drug commercialization is different from the non-orphan drug in terms of less marketing efforts, fast market penetration and 7-year market exclusivity; the patients advocacy group plays an essential role in assisting clinical trials and marketing; the most important is the Orphan Drug Act which simulates the cooperation among different organizations to accelerate the study and development orphan drugs. In the next chapters, a computational model is built based on the research questions and the conceptual model proposed in Chapter 2, 3 and 4. To start with, Chapter 5 will introduce the framework that used to seek answers to research questions.

Chapter 5 Research Design

5.1 Introduction

The majority of social science research is theoretical, and can be categorized in three ways: textual form, equation and computer program. The first two types are widespread in the social area, and through them social scientists have adopted either induction or deduction as their research reasoning. Social simulation presents another form of the reasoning process that combines induction and deduction. Computer simulations are viewed as a 'third way' of carrying out social research (Gilbert and Troitzsch 2005).

The application of computer simulation to social science is a breakthrough, through which researchers are able to use experimental methods to study the social phenomena. Simulation, carried out through modelling under varying conditions and parameters, is viewed as a sort of experimental methodology to some extent. Experimental research is difficult to carry out in most areas of social sciences. Thus, there are obvious advantages to simulation in exploring the casual relationship and interdependencies in social science domain. Section 5.2 will introduce the methodology of social simulation, including the type, logic, process, validation, and verification of modeling.

The book 'An Evolutionary Theory of Economic Change' by Nelson and Winter introduced the evolutionary economics or Neo-Schumpeterian economics. It focuses on the relationship between economic change and innovation. Since the 1980s, Agent-based Models (ABMs) have become the most important formal modeling methodology in this area. In section 5.3, the general features and methodological issues of ABMs are discussed. Section 5.4 provides a brief introduction about industry evolution and dynamics, and analyses the essential feature and methodology of History-Friendly Model. Section 5.5 introduces the origins and backgrounds of the genetic algorithms, such as the theory of

evolution and genetics, and then describes the procedures of genetic algorithms and some important issues about the design and application of genetic algorithms. Section 5.6 introduces the modeling toolkits of ABM and how to use Swarm and NetLogo to build ABMs.

5.2 Social simulation

Social simulation refers to a research field that applies computer simulation to study social phenomena. The simulation was initially emerged and developed in the natural science field, but is becoming more and more influential in the research area of economics, psychology, sociology, political science, linguistics, *etc.* The application of simulation in social science doesn't have a long history, and it can be traced back to the 1960s. Since then, social scientists have become increasingly interested in the computer simulation, which crosses the gap between the descriptive approach used in social science and the formal approach used in the natural sciences through moving the focus towards the process, mechanisms, and behaviors that build the social reality.

The Application of Social Simulation

The connections between social science and computer simulation are mainly methodological in character, and social science can benefit a lot from the simulation (Davidsson 2002). Firstly, social scientists convert social theories to computer programs, and then apply computer simulation to simulate social processes and carry out experiments that are impossible to do in the real world. Social simulation is especially helpful when the phenomenon to be studied is not accessible or is difficult to observe directly.

There are two primary applications of simulation in social science. The first is 'understanding', whereby the model can contribute to the understanding of the social phenomenon. The simulation model simplifies the complex real world rather than reproducing it. 'Prediction' is another main application of the social

simulation. Once a model can reproduce the features and dynamics of some social phenomena, it can be used to ascertain the future.

The Validation of Social Simulation

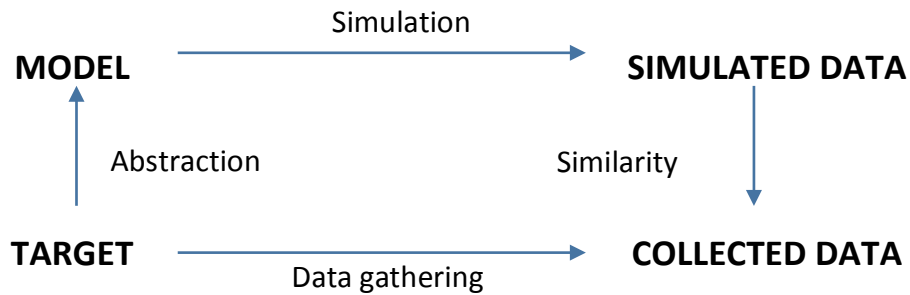
The validation of computer simulation in the social science is based on two components: the natural science and the underlying theory. In the natural sciences, the computer simulations focus on reproducibility, but this is difficult to achieve in the social sciences. Compared to natural sciences, the application in social science is still in its early stage and at a state of transition. The knowledge produced from the model is reliable if the model that is constructed to reproduce the dynamics is correct in the natural science. However, in social simulations, the validation of knowledge relies on the exact imitation of the characteristics of social dynamics.

The validity of social simulations depends on the purpose of the model (Küppers and Lenhard 2005). The main objective of social simulation is to describe the actual dynamics and complexities of the real world. Through computational experiments, social simulations reproduce the characteristics of the social phenomenon described by the theoretical model. Simulations are based on theoretical models that guide the simulation but do not determine it. On one hand, it is obvious that simulation can be realized via the underlying theoretical explanation; on the other hand, if the simulation can imitate the dynamics and complexities of the social phenomenon through data and experiment, then it can be considered as successful (Küppers and Lenhard 2005). Many of the social simulations aim at the prediction, so the fit between observed and simulated data are used to validate the prediction.

5.2.1 The Logic of Simulation

The process of simulation begins by identifying a specific social phenomenon as the target. Although the models are always simpler than the research targets,

the models should be sufficiently similar to ensure the knowledge produced by models can be applied to explain the research questions. If the simulated data are similar to the collected data, that implies that the outcomes generated by the model can explain and predict the real social world (Figure 23).



(Source: Gilbert and Troitzsch 2005)

Figure 23 The Logic of Simulation as a Research Method

5.2.2 The Processes of Social Simulation

Based on the logic of the simulation, the process of social simulation research can be outlined as follows:

Model Design

The first and most crucial step of social simulation is to establish clear objectives and research questions, which can help researcher focus on the social phenomena of interest and determine the correct simulation tools. The estimation of the parameters is essential for the simulation of the complex social phenomenon. To build a simulation model every parameter must be assigned an appropriate value, which is not easy. The vagueness of what the parameter represents will lead to the confusion of the simulation.

Models simplify the real social system. It is difficult to decide which factors to include for designing the model. If the model contains more parameters, it will

be more detailed and hence will imitate the real social system more closely. Conversely, it is risky to design a model that is more detailed than necessary, as it can over-complicate data collection and processing, which will influence the validation and verification of the model and the conclusion drawn from simulation (Gilbert and Troitzsch 2005). However, an abstract model that includes little information will also cause two gaps in interpretation. The first gap is between the target and conceptual model, while the second gap is between the outcomes of the model and the conclusions derived from the model. If the main objective of simulation is to predict the real social system, then it is essential that the model is not only accurate, but also simplistic enough to understand the social system (Axelrod 1997).

Model Construction

The process of constructing a model is a form of theory development, including refining and translating the theoretical basis to a more precise procedural form such as computation program. Researchers can program the model through modelling toolkits or self-written codes in computing languages such as C, C++, Objective C, Java, Prolog Smalltalk and Lisp. The choice of programming language depends on the type of model and the attributes critical for research.

Model Analysis

Simulation models generate large sets of data while avoiding the problem of missing data and confounding variables (Axelrod 1997). Researchers can study the influence of the specific factors by changing the parameters in the model, which contribute to our understanding of the real world. For example, it is interesting to study how a certain parameter will change over time if the parameter is assigned a different value. Furthermore, researchers can compare different versions of the model by changing the mechanisms of agents' activities. The effect of the different mechanisms can be analyzed by running controlled experiments.

Validation and Verification

Given that the application of simulation is increasing in problem-solving and decision-making, it is important that the results of the simulation are correct and accurate. These are concerns that can be addressed in terms of model verification and validation.

From Figure 24, it is evident that the verification and validation process are embedded in the round-link chain of problem entity (research target), conceptual model (logic and mathematical representation of the target), and computerized model (program) in the natural science simulation (Sargent 2005).

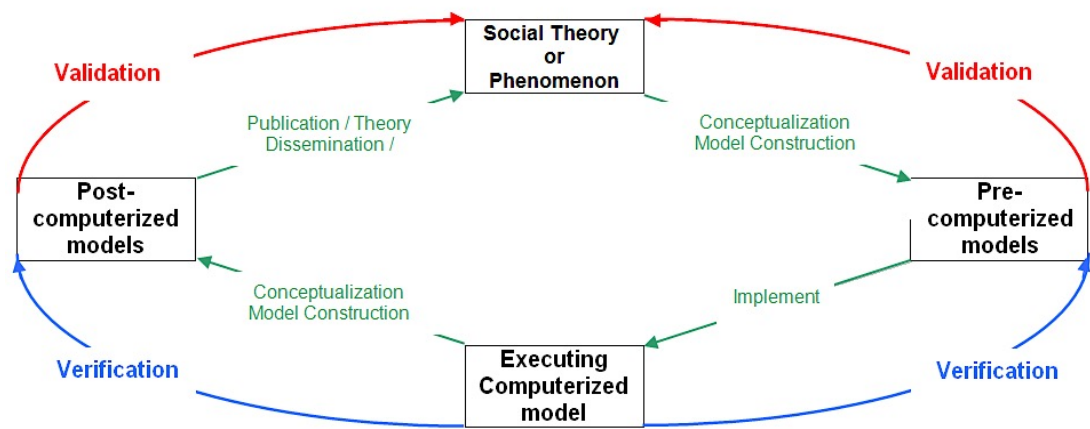


Figure 24 The Development Process of Social Simulation

The evaluation of these systems is also quantitative in nature. However, the evaluation of the social model is also qualitative. The conceptual model can be divided into two kinds: the pre-computerized model representing the target social theory and phenomenon, and the post-computerized model constructed on the computerized model and used to explain and predict (David 2009).

Computerized Model Verification ensures that the computerized model has been implemented adequately to coincide with the content and intention of the conceptual model.

Conceptual Model Validation confirms whether both the pre- and post-computerized model was established adequately to correspond with the target social theory and phenomenon.

5.2.3 The Type of Social Simulation

Social simulation is the general class of methodology for studying social issues using computer modelling. There are five major sub-types of social simulation.

System Dynamic Model is used to explain economic growth at the macro-economic level. Being a simplistic model, it usually has only one agent that is of low complexity, and only one level, either the macroscopic economic level or the social level. The model uses the difference or differential equations, in which the future state of one variable is dependent on the current state. The system dynamic model only provides equilibrium values for the variables.

Micro-analytical simulation is widely used in social policy interventions. It uses a random population cohort with a large sample size to calculate the aggregate statistics and subsequently estimate the future characteristics of the population (Gilbert and Troitzsch 2005). The policy intervention can be analyzed because there are two levels and a number of agents with higher complexity in the model. The primary use of the micro-simulation is to predict fiscal distribution, and the results of the micro-analytical simulation have influenced the policy-making in the areas of pensions and graduate taxes. However, the micro-analytical simulation cannot model the interactions between individuals. Moreover, the motivations and intentions of individuals are disregarded in the simulation.

Multi-level simulation is used to understand the individual behaviors that rely on the attributes of the overall population. Within the model, the complexity of the agent is low, and the number of agents is high. The interactions among the agents are simulated in the model; most of the interactions are linear and

simple. The individual's attributes in the current time step are evaluated based on the values of the population's attributes in the previous time step.

In the 1990s, the field of social simulation changed dramatically because of the development of multi-agent simulation that provided the opportunity to simulate autonomous individuals and the interactions among them. Distinct from the conventional statistical methods for analyzing the social system based on the assumption of the linear relationship between the variables and the conventional simulation model based on that agents are not autonomous and heterogeneous, multi-agent simulation stems from the research of nonlinear dynamics and artificial intelligence.

The linear assumption is very restrictive, because research targets in social sciences are always dynamic entities that change over time and react to other entities in the environment. A key feature of social phenomena is that every agent follows the simple rules of that system, which aggregate to produce its complex behavior. Simulation is the best way to analyze such complex systems.

Distinct from other social simulation models, multi-agent simulation contains more agents and exhibits higher complexity. A multi-agent simulation is composed of heterogeneous agents in a virtual environment. The agents in the model have four properties: autonomy, social ability, reactivity and pro-activity (Wooldridge and Jennings 1995). The agents have attributes such as knowledge and belief (correct and possibly incorrect information about their environment), inference (inferring further information from brief), social model (learning the interrelationship between other agents), knowledge representation (representing their beliefs), goals (actions are driven to satisfy their goals), planning (scheming actions according to goals), language (passing information for interaction) and emotions (emotional states interaction with goals) (Gilbert and Troitzsch 2005). The agents in multi-agent simulation are developed with an appropriate degree of autonomy, which enables the agents to act and react to the environment and other agents. With the development of computer science,

simulation can model the complex social phenomenon like learning and evolution process of a heterogeneous population.

5.2.4 Agent-Based Modeling

Agent-based modeling explores the collective behavior of agents obeying certain rules in the multi-agent system. In the social research area, the Agent-Based Model (ABMs) is the convergence of social science, computer science and agent-based computing (Davidsson 2002). ABMs have been used in social science areas, such as politics, sociology, and economics. As discussed earlier, the social simulation model can be abstract or descriptive, positive or normative, artificial or realistic, spatial or network, and complex or simple agents. Most agent-based simulation is positive, descriptive and analytical of social phenomena for the purpose of understanding it, while the normative model is designed to provide advice for the policy-maker.

In economics, there is an upsurge in the use of ABMs to explore various phenomena. The neo-classic economics assume that: 1) the economy is not in an equilibrium state; 2) the economic agents are homogenous with hyper-rationality; 3) all their behaviors are based on the maximization principle. The evolutionary economics does not assume the characteristics of homogeneity, rationality, and equilibrium; instead, it focuses on the disequilibrium processes, which emerge from the heterogeneous and bounded-rational economic agents. Nelson and Winter are important contributors to the field of evolutionary economics and pioneered the development of ABMs with heterogeneous agents to explain the evolution of industry. Since then, many more ABMs have been used to explain different economic phenomena, including the industrial evolution.

Computer simulation techniques enable agents in ABMs to have a high degree of heterogeneity. Agents are not isolated but connected with other agents; various networks are embedded among them. The agents in the model can not only

interact with each other but also endogenously learn over time. These agents do not have objective functions or a static environment, so their objective is not to maximize the functions amidst constraints but rather to develop with bounded rationality. Different agents have different behavioral rules that modify over time to match to their changing environment. ABMs are path-dependent, so their agents' behaviors rely on their statuses in the past. As the agents are bounded rational, they can accumulate the ability of R&D or marketing by learning from past experiences. For the learning process, ABMs in economic apply simulation methods such as genetic algorithms and the NK model (Kauffman 1993).

The selection mechanism is the core of analyzing the evolutionary economics. The most common selection mechanism is driven by the competition within the market. Firms compete with each other in the market; some of them survive while others may be forced out. Another force of selection is science and technology. The selection mechanism is dynamic rather than static, because while the market and science are always changing, the routines of firms may vary to suit these changes as well. Firms are continuously modifying their strategies to survive in the industry. The ABMs can simulate the selection mechanism through a continuous disequilibrium, macro-micro loop and path-dependency (Yoon and Lee 2009). Moreover, ABMs can generate continuous novelties endogenously or exogenously, such as the emergence of new type of organizations, behavior or products. According to these characterizations, ABMs can achieve a deeper understanding of social phenomenon by predicting future and performing experiments that cannot be carried out in reality.

The basic structure of ABMs is:

a. Time t

Most of the ABMs are built based on the discrete time $t=1, 2, \dots$

b. Agent $A_i = \{A_1, A_2, \dots, A_N\}$

The model is composed of a set of agents at each time step, and the number of agents changes over time. For instance, the entry of new firms increases the total number of agents, while the exit of unsuccessful firms decreases the number.

c. Micro state $S_{i,t} = \{S_{i,t}^1, \dots, S_{i,t}^J\}$

Each agent A_i is characterized by a certain number of microstates. These variables can be endogenously modified by agents' behavior.

d. Micro parameter $\delta^h_i = \{\delta^h_{i,1}, \dots, \delta^h_{i,H}\}$

Each agent A_i is also characterized by micro-parameters, which contains the information about the behavioral and technical characteristic of A_i . The value of these parameters cannot be modified endogenously but can be influenced by exogenous changes.

e. Macro parameter $\theta = \{\theta_1, \dots, \theta_J\}$

The whole system has many specific characteristics, which are evaluated by macro-parameters in the model. The macro-parameters cannot be modified by agents endogenously; the researchers can change the value of parameters in the process of simulation.

f. Interaction pattern

The interactions among agents can be shown by a network graph. Each agent is presented as a node, and the line linking two nodes means those two agents interact with each other. The interactions are changing in the process of simulation, or remain time-invariant.

g. Behavioral rules $\mathcal{R}_{i,t} = \{\mathcal{R}_{i,t}^1, \dots, \mathcal{R}_{i,t}^B\}$

Each agent in the model has a set of behavioral rules that affect the micro-status of the agent. The behavioral rules simulate the way of decision-making of each agent; different agent has the different set of behavioral rules. The behavioral rules are not time-variant, they can be modified endogenously or exogenously.

h. Aggregate variables $Z_t = \{Z_t^1, \dots, Z_t^K\}$

The aggregated variables of micro-variables or the macro-variables influences the micro-statuses of each agent through the macro-micro loops, they can be used to analyze the results of the simulation.

Since Nelson and Winter started using ABMs to explain evolutionary economics, ABMs have gained widespread use in many areas of social sciences. However, they are not the perfect modelling methodology either due to several limitations. ABMs have many methodological issues, such as its arbitrary assumptions and calibration (Yoon and Lee 2009). The arbitrariness of ABMs has undermined the validation of the models. Many contributions to deal with the arbitrariness problems of ABMs have been made (Pyka and Fagiolo 2007), to make ABMs more historically sensitive may be another solution. A number of ABMs are ignorant or lack the historical evidence, so they hold value on a theoretical level but still need the empirical validation. Some of the parameters in the ABMs can be calibrated by real data. In other situations where this is not possible, the modelers calibrate the values of parameters arbitrarily, which influences the robustness of the results. In addition, there is no standard procedure of model building and analysis. With the advance of computer science and more applications of ABMs, researchers have intended to design procedures to overcome the limitations and to integrate other modeling methods to improve ABMs. History-friendly model is one of the distinctive attempts to advance the methodology of ABMs.

5.3 History Friendly Model

The publication of “An Evolutionary Theory of Economic Change” by Nelson and Winter in the 1980s shifted the field towards a new approach that emphasizes on the dynamics and evolution. Much work regarding this has raised a number of issues. Nelson and Winter also introduced the modelling tools of evolutionary economics, known as ABMs, which are not specially primed for exploring evolution in economics. Thus, researchers developed new methods to overcome the limitations of ABMs. For example, the developers of History-Friendly Model

(HFM) bridged the generic formal models with appreciative theories by incorporating historical details of these theories into the models (Yoon and Lee 2009).

The HFM is a formal modelling tool based on the theory of evolutionary economics that specifically focuses on industrial evolution and dynamics. According to Malerba and Orsenigo (1996), there are three levels in analyzing industrial evolution and dynamics: the first level is industrial dynamics; the second level is structural dynamics; and the third level is structural evolution. The first level refers to the specific features of the industry such as the growth and distribution size of firms. The second level refers to the dynamics of structure in the industry life cycle such as the entry, exist, and concentration. Apart from the dimensions mentioned in previous levels, the structural evolution approach focuses on the evolution of the industry over time, including the emergence of the new industry, the changing boundaries of firms, the generation and transformation of science and technologies, the development and change of firm competence, the networks and the role played by different organizations (Malerba and Orsenigo 1996).

The analysis of the structural dynamics of industries regarding entry, exit, firm's size and growth, product and process innovation does not give us a deep understanding of many issues about the evolution of industries. The third level is a broader and more complex level of analyzing the evolution of the industries. First, it highlights the transformation of existing products and innovation processes, the emergence of new technology and applications of technical advance in different ways. Moreover, in some cases the emergence of new industry is from the existing industry and science. In other cases, the new industry is not related to the past and composed of new firms. Besides, the organization and boundaries of firms are changing continuously throughout the evolution of an industry. New entrants may appear on the scene, with some exiting and others surviving and growing. Therefore, the existing firms will change their strategies and structures. Finally, relationships among different

organizations significantly shape the industry. These relationships concern the connections among firms, suppliers, buyers, universities, governments and public organizations. During the process of evolution, new relationships will emerge; some relationships may merge while others may disappear.

The model of structural dynamics is mostly unexplored, partly due to theoretical and methodological difficulties. The main reason for modeling of industrial dynamics is the lack of the empirical study of the phenomenon and the understanding of the mechanism of industrial evolution. To develop an empirical understanding of structural evolution, we need to take the historical account of the industry. At the preliminary level, some key features of the phenomenon should be identified: type of phenomena, time-scale we want to study on, and how the phenomena is linked to different time-scales. Simulation techniques appear to be a method to address these problems.

5.3.1 The Applications of HFM

HFM (History-Friendly Model), first proposed by Malerba and Orsenigo, is an empirically and historically-founded theory of exploring the industry evolution, economic change and technology dynamics. It is useful in explaining the industrial evolution in sectors such as the computer and pharmaceutical industries. Malerba, Nelson, Orsenigo, and Winter explored the effects of policy on the structure of computer industry (Malerba, Nelson et al. 2001). Malerba and Orsenigo explored the long-term dynamics of market structure and innovation in the pharmaceutical industry, and discussed different situations of patent protection in the age of random screening (Malerba and Orsenigo 2001). Malerba and Orsenigo explored market structure in the dynamics of the pharmaceutical industry and biotechnology industry, the model replicating the main patterns of industry evolution including the demand, the types of competition and the period of random screening and in the period of molecular biology (Malerba and Orsenigo 2002). Pyka and Saviotti applied HFM in the biotechnology sector to show the evolution of innovation networks in the

biotechnology-based industries, highlighting the importance of outsourcing new capabilities from other companies either through partnering or radical research (Pyka and Saviotti 2001).

Although the primary application of HFM is to analyze the evolution of a specific industry, there is a broad area for HFM to explore. Fontana, Guerzoni and Nuvolari (2008) developed a model exploring the influence of different patterns of demand and technological opportunities on the industry evolution in the UK and US in the course of the nineteenth century, the model stretches the application of HFM far from the high-tech industries to manufacturing industry (Fontana, Guerzoni et al. 2008). These applications of HFMs are only the prelude of its application, and there are still many opportunities to exert the model.

5.3.2 The Characteristics of HFM

The HFM belongs to the family of multi-agent based simulation, so it can be considered as one variant of ABMs (Yoon and Lee 2009, Garavaglia, Malerba et al. 2010), as it shares the same features of ABM, such as bounded rational agents, learning process, interactions with other agents, path-dependency. However, it has its own unique features, too:

HISTORY Orsenigo, one of the developers of HFMs pointed out that the evolutionary economics is based on empirical and historical case studies similar to the biological evolution theories (Orsenigo 2007). The history of a specific industry plays a vital role in HFMs. Model building and calibrations are guided by historical evidence. ABMs have their weaknesses in the arbitrariness of assumptions and calibrations, but HFMs are built through continuous communication with appreciative theories, and basic assumptions can be justified by the observed history. HFM cannot replicate every detail of history, as not all variables can be obtained in the real world and some of them need to

be simplified or eliminated for the efficacy and effectiveness of the model. Through trial and error experiments, the modeler can search for the best set of parameter values to replicate the stylized facts in the history, and this set is called standard set. In summary, history provides two methods for evaluating HFMs: consistency of assumptions and consistency of simulation results with historical evidence.

SPECIFIC Although HFMs can be built on a national or global level, they are focused on a certain period of history. Science and technology, institutions, policies, products and market conditions are different in terms of time and geographical location. Neo-classic economics explain heterogeneous economic phenomena under the same framework, but evolutionary economics take the historical and geographical account into the explanation. Drug commercialization in the US is different from U.K., and the mechanisms of orphan drug R&D before the 1980s were different from after the 1980s. So, history and geographical location are important in explaining agents' behavior in evolutionary economics. To capture the historical and geographical specificities, different HFMs are required. For instance, Malerba has built one HFM to describe the pharmaceutical R&D process based on random screening, and other models to replicate the R&D process based on molecular biology.

CALIBRATION HFM provides an important way to calibrate the model. The arbitrariness of ABMs is due to the lack of historical evidence, but the arbitrariness of HFM is mitigated in HFMs by calibrating the model with real data of industry history. The real data can be used in HFMs in two ways: the first is calibration and the second is validation. The real data are used to calibrate the value of parameters in the model, but all parameters cannot be calibrated from the real data because some parameters are unobservable in the real world.

5.3.3 Three-step of History-Friend Modeling

The methodology of the history-friendly model consists of three steps: The first step is to describe the history of a specific industry based on existing or appreciative theories which include brief surveys, theoretical background of focused factors and mechanisms influencing the evolution process. Based on the history of a specific industry, a model is built to replicate the history by a computational program and a set of parameters. The collection of parameters used to build the history-replicating simulation is called the standard setting. An HFM cannot replicate every detail in the history, as it only replicates several major features of the history according to selected appreciative theories. After a run of the history-replicating simulation, the last step is to build history-divergent simulation. In history-divergent simulation, the values of important parameters and the key assumption are changed; the outcomes influenced by different settings are observed.

5.3.4 The Shortcomings of HFMs

In all, HFMs cannot only be used to explain the evolution and dynamics of the industry but also to test the logic of policy heuristically, however, the application of HFMs in policy implication has not been very much addressed (Yoon and Lee 2009). The social system is a complex system, and the complexity is the core of the dynamic economic system (Pyka and Fagiolo 2007). But, the complexity is lost in the formal modeling. ABMs are developed predominantly with the complex system and evolutionary program (Yoon and Lee 2009). Some ABMs involve a certain level of complexity and use different mathematical methods to replicate the complexity in the real world. However, the current applications of HFMs don't employ a high-level of complexity, and some of the assumptions in the model are arbitrary. The family of HFMs still has a great potential to be developed, especially embrace the concept of the complex adaptive system.

5.4 Complex Adaptive System in Social Simulation

The concept of complexity is critical in explaining the socio-economic system, and to increase the level of complexity is one of the critical methods to improve the HFMs. Traditionally, many systems were treated as a linear system, like the mechanical system, biological system, and economic system, and the way we analyze them is through decomposition. However, with the growing knowledge, we found not all the system in the real world is linear, and not all the system management can be implemented by hierarchical decomposition. Most of the social phenomena are non-linear and dynamic; the elements are intelligent and interdependent. Decomposition cannot be used to address the complex system, as it may result in the loss of data about the interactions of elements. Therefore, it is necessary to address the system in a different way and from a different view of point—complex adaptive system.

5.4.1 Introduction

The characteristics of CAS are described in Chapter 2, including independent agents, non-linearity, emergent, and self-organization. Beside those, CAS is embedded in another CAS, so each individual agent in a CAS is itself a CAS. For instance, in pharmaceutical innovation system, a biotechnology company is a CAS and is also an agent in the CAS of the biopharmaceutical industry. Agents co-evolve with the CAS of which they are as a part. The interaction among them is mutual rather than one way; the entire system is emerging from a rich pattern of interactions.

The research of complex adaptive system does not consist of a single theory but rather embraces a number of theories. Historical data are the acute source of information because they play an important role in informing the future. Although the extents to which systems are history-friendly are various, complexity science validates the history data to the states of the system. However, the relevance of history doesn't imply there is no novelty in the

system. New elements or creative behavior can emerge in CAS at any time. Several tools are used to study CAS, such as, Markov chain that is the most general, evolutionary algorithms that run within an environment of a fitness function, and agent-based simulation that serves as a platform for imitating the dynamic characteristics of the real-world complex system(Chan 2001).

5.4.2 CAS model in orphan drug innovation

The computational model implemented by computer program represents the behavior of the social system. The model is an approximation, simplification of the real world. It consists of a set of variables, mathematical equations to stimulate the changes of the phenomenon. Because of the high complexity of CAS, traditional modeling methodologies are considered inadequate. The development of artificial intelligence and multi-agent based simulation has contributed a lot to the study of CAS (Cohen and Axelrod 2000).

The model inspired by the complex adaptive system is agent-based (agents are the main actors in the CAS model), so the agent can be a molecule, a person or an organization. Agents behave based on local and surrounding knowledge and conditions; they change other agents, and in the meantime, they are changed by other agents. The interactions and feedback loops between agents can create change or stability in the system. To better understand these complex systems, agent-based simulation is designed to simulate the complexity using tools as genetic algorithms, artificial neural networks, and other mathematical methods.

There are three key elements for complex adaptive system design: the first is creating environments in which the system can evolve naturally over time; then setting the simple rules and minimum specifications; and finally, providing broad boundaries for the natural creativity to emerge from the system (Plsek and Greenhalgh 2001). The model analysis process is also a process of model improvement. The data generated from simulation will be evaluated from the perspectives of accuracy and applicability (Sargent 2005). The comparison

between simulated data and real data is an important process of model validation.

5.4.3 The Application of CAS Models in Healthcare System

Our research objective is the orphan drug innovation system in the US, which can be considered as part of the healthcare system. In the past, some researchers in the healthcare sector considered the health care system as a machine. The mechanic metaphor shed lights on how the system can be studied: through breaking down the system into units, identifying the broken units, and replacing or improving it. Actually, due to the interactions and interdependences of system determinants, the health care system does not follow the simple linear mechanism; policy-makers should adopt new methods to design their interventions better. Recently, researchers and managers in the health care system are starting to apply new ways of designing health care programs and organizing health care services based on complexity science.

Even the social system is the most complex system, and the healthcare system is perhaps the most complex system in the domain of the social system. Healthcare system is composed of a large number of players, and it is embedded in other social systems, such as industrial and political systems. There is no uniform central control in the system, where the order is emergent. The system is adaptive, so organizations learn and adapt to new policies over time and behaviors converge to develop the novel collective pattern. Because of the diversity of organizations and interactions among them, the healthcare sector is an ideal field for the application of complexity science. Moreover, the CAS simulation is a productive means by which to apply complexity science to address health care issues (Dooley 2002).

Social science has begun to use the methods and metaphors from complexity theory since the early 1990s, and an increasing number of researchers explored the application of complexity science to study the organizations in late 1990s,

during the same period, the application of complexity science extended to the innovation. Until now, a large number of researchers have applied complex theory to explain the innovation system from various perspectives.

Begun, Zimmerman and Dooley analyzed the healthcare organization as a complex adaptive system from the perspectives of healthcare innovation and healthcare integrated system, their research focused on managing the relationships among organizations and motivating changes and innovations (Begun, Zimmerman et al. 2003). Plsek explored the spread of innovation in the healthcare sector—since the healthcare system is complex, how that complexity affects the generation and spread of innovations (Plsek 2003). Rouse emphasized the ‘information’ and ‘incentives’ in the healthcare system: the improvement of the system requires the stakeholders have abundant information about the whole system, information can be used to evaluate the situations in this complex adaptive system and drive the adjustments of incentives and inhibitions to stimulate stakeholders to alter their activities to provide high-value health care (Rouse 2008). Moore and other researchers modeled the precaution of changes in medical demand and evaluated the relevant policy actions (Moore and Moore 2011). Complex theory broadens and deepens the scope of study of the healthcare system, moreover, provides better insights to respond to the health system’s issues. However, all the research carves out the theoretical ground but rather offer the practical model.

5.4.4 Policy design for Social System

Policy-makers face big challenges in designing robust policy for the complex social system. Policymakers have always drawn on a wide range of sources of evidence in making decisions (Mays, Pope et al. 2005). The ideal policy-making process starts from setting clear objectives, and then finds the relevant information and possible solutions, at last devises alternatives to fit the objective. This process is based on the exploration and exploitation of the information.

Policy-makers should firstly create rich evidence base through studying the problem, then exploring alternative solutions and testing them in the system. To arrive at the agreement, stakeholders need to understand all the possible benefits and losses. The robustness of policy design requires an extensive exploration and exploitation of the internal and external factors that may influence the effect of new policies.

Designing the policy for the complex adaptive system is extremely difficult regarding the ambiguous objective, uncertain methods, diverse stakeholders and the difficulty to get access to information. In the complex adaptive system, the individual agent has the ability to adapt their behavior to the dynamic environment including new policies. The adaptation process is progressive; it takes time for the players to find the optimal strategy. Moreover, there are mutual interactions among different agents in responding to the new policy.

Policy design is a successive and endless process. On the one hand, the desired goals and values of policy are always changing. On the other hand, the dynamic environment of the system may lead to the changes in policy outcomes and produce unanticipated outcomes. Therefore, policy should not be made without amendments anymore but revised endlessly.

Policy issues for public health can be characterized as designing within a complex adaptive system (Holland 1992, Moore and Moore 2011). Public healthcare as a complex adaptive system of systems, policy design for such system requires an understanding of the various interests, actions, and resources of multiple stakeholders. Although the complex adaptive system cannot be controlled, it can be designed. The design of the healthcare system should start with the recognition that the system involves all stakeholder organizations, including customers, partners, competitors, channels or regulators. The current public intervention has faced significant challenges in addressing healthcare system, because it doesn't deliver the acceptable level of

satisfaction for all the stakeholders within or beyond the system. The malfunction of the current system is because of the complexity, which leads to the challenges of diagnosing and designing effective intervention for product innovation and improvement of current health care system.

Arriving at a robust solution requires the policy-maker to explore and exploit a vast number of information and relationships hidden under the scenarios in support of their solutions. The CAS model can simulate the various environments and interventions and the processes in which the possible outcomes emerge from the decisions of policymakers. Thus, the CAS provides potentialities for the policy makers to observe the intended and unintended consequences of policy alternatives.

5.5 Algorithms

The same as evolutionary economics, the evolutionary program is inspired by the Darwin's 'biological evolution' theory. The Darwinian principle of 'survival of the fittest' is the theoretical basis of evolutionary computation including genetic algorithms, evolutionary program, and evolution strategy (Fogel 1994). The theory of natural selection, first introduced by Darwin in 1859 in the book 'On the Origin of Species,' proposes that the plants and animals that still live today are the results of millions of years of adaption to changes in environment.

Natural variation exists among the individuals of any population of organisms. Many of these different traits do not affect survival, but some play a significant role in improving the chances of the survival of the particular individual. The traits that increase the survival of an organism will often lead to the rise of its reproductive rate. The advantageous traits can be passed from parents to children, although they cannot be passed to all the offspring, over many generations these traits will become dominant in the population. For instance,

some members of a population die; they are replaced by new members whose parents are better adapted to the environment. In this way, the natural environment of an organism 'selects' for traits with a reproductive advantage, causing the gradual evolution of life.

In the 20th century, genetics was integrated with Darwin' theory of natural evolution, and the evolutionary phenomena had been further explained in way of genetic mechanisms. Natural selection is the non-random process through which biologic characteristics of the population become more or less common because of the function of differential reproduction. Natural selection occurs through changes in heritable traits and acts on the phenotype-the complete collection of traits. Evolution processes give rise to the diversity of population; the genetic diversity existing in the population is a key factor in the evolution. Evolution also influences the form and behavior of organisms; the most important feature is the adaption that increases the fitness of an organism to the environment. The evolutionary process enables an organism to become better able to live in its environment.

5.5.1 Genetic algorithms

The genetic algorithms are an optimization and search technique based on the principle of natural selection and genetics. It was first introduced and investigated by John Holland in the 1960s and then developed by him and his students and colleagues in the 1970s. The original objective of genetic algorithms is not to deal with the specific problem, but rather to shed lights on the phenomenon of adaptation through the computational system. The first book 'Adaptation in Nature and Artificial Systems' of Holland published in 1975 introduced genetic algorithms in light of biological evolution and theoretical foundation for adaptation through GA.

Genetic algorithms are efficient, adaptive and robust search and optimization methods that are applied in large and complex systems. In the last decades,

there have been extensive interactions among researchers. It has been widely and successfully used in simulating the living system of biology, sociology, and economics. Some classic applications include scheduling (Hou, Ansari et al. 1994, Gonçalves, Mendes et al. 2008), stock market trading (Conrad and Kaul 1998, Allen and Karjalainen 1999) , transportation (Potvin 1996, Altiparmak, Gen et al. 2006), drug design (Douguet, Thoreau et al. 2000, Terfloth and Gasteiger 2001).

5.5.2 Biological Background

The genetic algorithms were inspired by the evolution of the natural world. Nature has a powerful population-based evolution mechanism of optimization process (Fogel 1994). Genetic algorithms use some biological terms in the spirit of analogy with biology in reality.

All living organisms are composed of cells, each of which includes the same set of chromosomes (Figure 25). A chromosome is a string of DNA, and it can be divided into genes- the functional blocks of DNA. DNA encodes a particular type of protein that determines a trait in the organism, such as hair color. The different possible settings (black, blonde, red) for a trait are called alleles. Each gene has a particular locus on the chromosome and holds the information to build cells and pass genetic traits to offspring. The total complement of all chromosomes in an organism is called the genome; a particular set of genes in a genome is known as genotype.

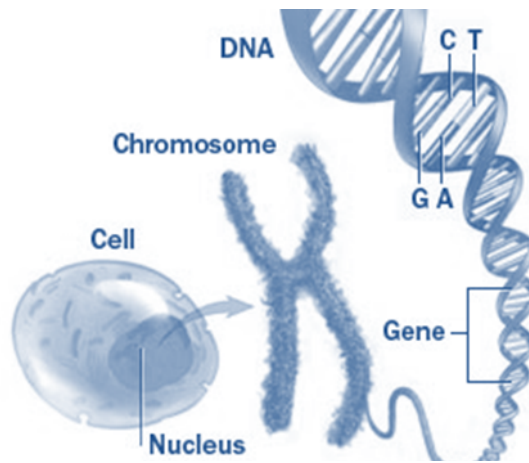


Figure 25 The Biotechnological Structure of Cell

5.5.3 Genetic Algorithms

Genetic algorithms are modeled on the principles of natural evolution system to solve complex optimization problems. In genetic algorithms, chromosome means a possible solution to a given problem, with most of them encoded as a bit string. The gene is a single bit or some adjacent bits that encode a specific element of the possible solution. The allele in a bit string is either 1 or 0. Crossover typically exchanges the subparts of two single chromosome parents; mutation randomly changes the allele values of one or more locus of the chromosome.

As shown in Figure 26, the procedures of GA are typically implemented as follows:

- 1) **Translation** The problem to be solved is defined and translated to an evaluation function that indicates the fitness of any candidate solution.
- 2) **Initialization** A population of candidate solutions (chromosomes) is randomly generated subject to specific constraints.

- 3) **Evaluation** Each chromosome in the population is decoded into a form appropriate for evaluation and is assigned a fitness score according to the objective.
- 4) **Selection** Each chromosome is assigned a probability of reproduction; it refers to the likelihood of selection. The higher fitness a chromosome has, the more it is likely to be selected to reproduce.

According to the assigned probability of reproduction, a new population of chromosomes is generated by selection from the current population. The generation is via specific genetic operator: crossover and mutation.

- 5) **Crossover** This operator selects a locus and exchanges the subsequence between two chromosomes to generate two offspring with possibility P_c . For instance, two 8-bit binary strings 10000001 and 11111111 are crossed over from the third locus in each to generate two offspring 10011111 and 11100001. Without crossing-over, the offspring are precisely the same copies of the parents.
- 6) **Mutation** This operator randomly alters more than one bit in a chromosome. For instance, the string 11100001 is mutated in its fifth locus to produce 11101001.

7) The new generation of chromosomes is created.

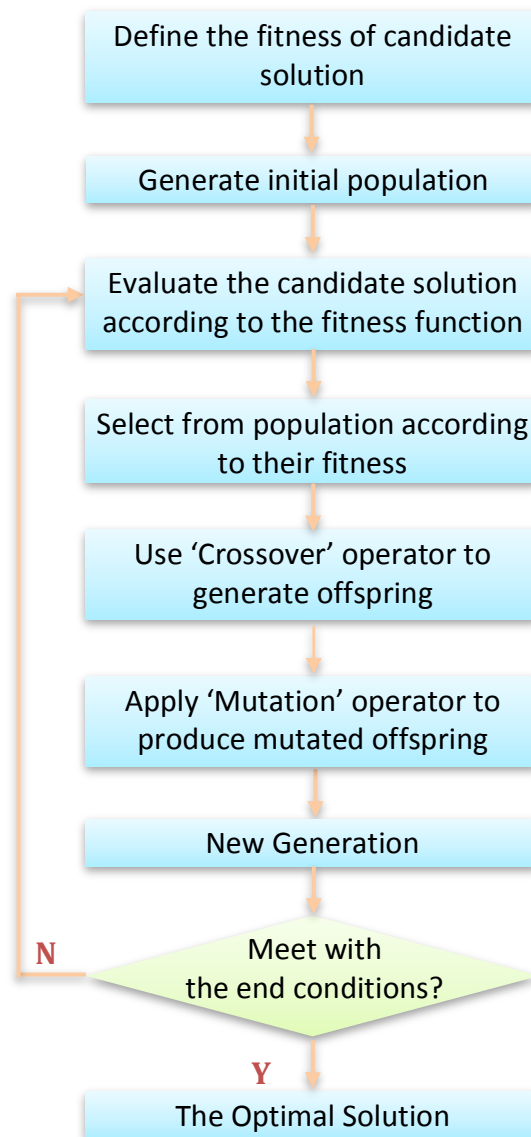


Figure 26 The Flowchart of a Binary Genetic Algorithm

8) The process is ceased once a suitable solution has been found or if the available computing time has expired; otherwise, the process continues to proceed to step 3) where the new chromosomes are evaluated, and the cycle is repeated.

9) The output of the GA is the best solution in the population when the simulation ends.

Some issues must be addressed when designing a genetic algorithm.

5.5.3.1 Binary Encoding

Encoding is the central factor in the success of genetic algorithms. Binary encoding is the most common encoding, while other applications use the alphabet character or real number to form chromosomes. Binary encoding is widely used because the genetic algorithm was developed based on such encoding and some GA applications tended to follow this lead. The theory has been applied to non-binary encodings, but such extensions are not as well developed as the original theory.

5.5.3.2 Selection

According to Darwin's theory of evolution, the fittest one can survive and generate new offspring. The problem is how to select the better individuals in the population. The most commonly used methods of selection are: Roulette Wheel Selection, Rank Selection, Tournament Selection and Elitism Selection.

Roulette Wheel Selection selects parents according to their fitness. Members with more significant fitness value will be chosen more often. For instance, all the members of the population are placed in the roulette wheel, and each one is allocated a place according to its fitness value. The better the solution, the more places are allocated and the bigger possibility to be chosen.

Rank Selection firstly ranks the population according to the fitness value, and then every member of the population receives new fitness value. The new fitness of the worst one is 1, the second worst is 2, ..., and the best one is N (N is the number of population members). This method leads to slower convergence

because the differences in fitness value among members are not as big as in Roulette Wheel Selection.

Tournament Selection starts with choosing a certain number of individuals and runs several 'Tournaments' among them. The winner of each tournament is selected. The outcome of selection can be adjusted by changing the size of the tournament. The larger the tournament, the less chance that weaker members are selected.

Elitist Selection copies the member with highest fitness from parents to the new generation; the rest is done in a classical way. When generating new offspring through mutation and crossover, there is a significant chance of losing the best solutions. Elitism increases the performance of GA by preventing the loss of the best solutions.

5.5.3.3 Evaluation

The individuals in the population are evaluated by an evaluation function, which is defined by users according to the problem they want to solve. The evaluation function acts as a link between genetic algorithms and the problem. The fitness value of each individual is the outcome of the evaluation.

5.5.3.4 Genetic Operator

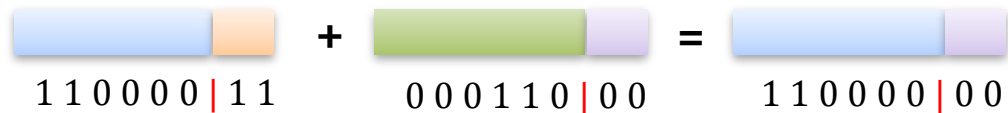
Crossover and mutation are two basic operators in Genetic Algorithms. The implementation of operators depends on the problem itself and the coding. We introduce the genetic operators based on binary encoding.

Crossover

The crossover operator has been considered as the distinguishing feature of genetic algorithms. The idea behind crossover is that the new generation is likely better than their parents by recombining the best characters from both

parents. It takes place during the evolution based on a user-definable crossover probability. There are many ways of crossover.

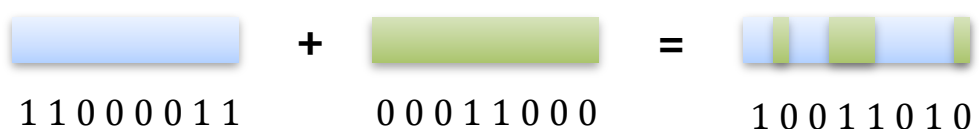
Single Point Crossover selects one crossover point (red line), copies the binary string from the beginning to the crossover point from one parent (blue rectangle), then copies the rest from the second parent (purple rectangle).



Two Points Crossover selects two crossover points (red lines), copies the binary string from beginning to the first crossover point from the first parent (red rectangle), then copies from the first to the second crossover point from the second parent (green rectangle), finally copies the rest from the first parent (orange rectangle).



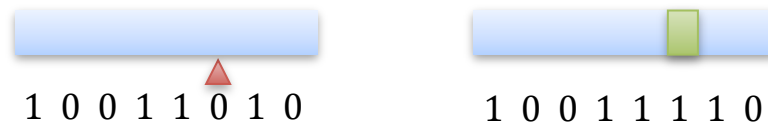
Uniform Crossover doesn't have fixed crossover point; bits are randomly copied from the first (blue rectangle) and the second parent (green rectangle).



Mutation

Mutation is a crucial genetic operator that alters one or more of the bit gene values in the chromosome. This operation can result in an entirely new chromosome, with which the genetic algorithms can arrive at a better solution. The objective of mutation is to maintain the diversity within the population and

inhibit premature convergence. The probability of mutation among individuals in the population is very low, only a small portion (usually $P_m=0.1\%$) of individuals will have some of their bits flipped. If P_m is set too high, the algorithms will turn into to a random search.



The effects of different genetic operators are different. If there is only selection without any genetic operators in the process of genetic algorithms, the new generation is always the copies of best individuals from the population. Using selection and crossover will lead to the algorithms to converge on a good but not the best solution. If only using mutation, the algorithms are similar to the random walk through the search space. If using selection and mutation, the algorithms are similar to hill climbing algorithms that starts at an arbitrary solution and then tries to improve the solution by incrementally changing a single element of the solution (if the solution is better, the change is made to the new solution; if the solution is worse, the origin solution is kept).

Since population contains thousands of information (knowledge), genetic algorithms combine the good information in a solution with good information from another solution to create a better solution with good information inherited from both parents. Via the combination of selection, crossover, and mutation, genetic algorithms converge over successive generations towards the global optimum. These operations produce a fast, powerful and robust technique because genetic algorithms integrate direction and chance in the process of optimization in an effective and efficient way.

The evolution is a method for designing innovative solutions to the complex system (Mitchell 1998). Genetic algorithms are different from most of the typical optimization in the following ways: first, genetic algorithms deal with more than one point at the same time, not with a single point; second, genetic

algorithms work through sampling (blind search) based on payoff information; third, genetic algorithms use stochastic operators to improve the outcome, not deterministic rules; forth, it can be used to adapt solution to changing environment, in contrary, traditional methods are not robust to dynamic changes. However, genetic algorithms are not the best way to solve every problem. For instance, traditional methods can find the solutions quickly sometimes for the problems that are not very difficult (Haupt and Haupt 2004).

5.6 Swarm and NetLogo

Multi-agent based models have been proved to aid our understanding not only on the natural phenomenon but also on the social phenomenon. A steady and sharp growing use of multi-agent-based simulation accelerates the growth of software platform for modeling. Recently, an increasing number of Agent-Based Software Toolkits (ABST) have become available for agent-based modeling, for instance, NetLogo, Swarm, Repast, MASON, Ascape, and Anylogic. The aim of these toolkits is to (1) provide a certain level of abstraction in which users can develop their objects; (2) incorporate some features of visual programming that make the development easier; (3) have run-timing tests and debugging environments; (4) allow users to use the objects created by library or other users (Serenko and Detlor 2002).

5.6.1 The Comparison of ABST

Nowadays, more than one hundred toolkits are developed for ABMs. There are four popular agent-based modeling toolkits: NetLogo, Swarm, and RePast. Each of the toolkits has a variety of characteristics (Table 13).

Table 13 The Comparison of ABSTs

Toolkit	Scalability	Execution Speed	Programming Language	Primary Area	Main Feature
NetLogo	Desktop computing	Intermediate	NetLogo	Social and natural Sciences	User-friendly Good visualization
Swarm	Large-scale	Slow	Objective C; Java	General purpose	Stable and clear but difficult to use
Repast	Large-scale	Fast	Java; C++; Python	Social Sciences	Versatile but need a massive amount of Java knowledge
MASON	Large-scale	Fast	Java	General purpose	Faster than Repast

Swarm is the precursor to other toolkits. Compared with NetLogo and MASON, Swarm, as the founder of ABM and library is stable, relatively small-sized and well-organized with various set of tools, clear conceptual basis and intelligence design. It has been designed for extensive uses across the scientific domains of chemistry, physics, ecology, sociology, economics and political science. Swarm is a powerful too, but users should be experienced in Objective C or Java and familiar with object orientation methodology and learn some Swarm code.

MASON was developed as a smaller and faster alternative to Repast, and it demands a significant amount of Java knowledge on its users. NetLogo has its own programming language that is easier to start than Java and Objective C; moreover, it has a very accessible model library in which models can be extended. It's believed to be by far the most professional platform in its appearance and documentation (Allan 2009). A review identifies that NetLogo is well designed and documented and very easy to learn and use while Repast is the platform that is recommended for models that are especially demanding computationally or not well-fitted to NetLogo conceptual framework (Lyтинен and Railsback 2012). In the following sections, the most mature ABST--Swarm and the simple but powerful ABST – SWARM and NetLogo are introduced.

5.6.2 Swarm

Swarm, originally developed at the Santa Fe Institute, is a software package for Multi-Agent Based Simulation of the complex system. It is free and available from <http://ftp.swarm.org>. Swarm contains a set of libraries that user can choose and call features; it helps users to develop the model through well-defined protocols and powerful tools. It was initially developed for multi-agent simulation of CAS (Zheng, Son et al. 2013). Since its first release, it has become one of the most famous, widespread and influential simulation frameworks (Haupt and Haupt 2004).

In the Swarm model, there are some agents, some agents representing the actors and environment; others are used as tools to facilitate the modeling process and set/collect information of the simulation. Once objects are created, they interact with other objects based on their states and rules of behavior. The structure and program of Swarm are introduced in Appendix 1.

5.6.3 NetLogo

NetLogo is designed as a multi-agent programming language and modeling environment for simulation of natural and social phenomena. It was developed by Uri Wilensky in 1999 and has been improved continuously at the center for Connected Learning and Computer-Based Modeling at Northwestern University. It is originally developed to allow StarLogo models, another ABMT developed by MIT, to be developed on computers using Macintosh Operating System (Castle and Crooks 2006). It has been applied to develop models in areas ranging from biology and physics to the social sciences.

NetLogo is best suited for modeling complex system over time. Users set up 'agents' and give 'commands' to them to let them operate independently. This enables the model explore activities between the micro-level behavior of

individuals and the macro-level patterns that emerge from their interactions. How to build a Multi-Agent Model by NetLogo are presented in Appendix 2.

5.7 Summary

Nowadays we can see complexity is everywhere, but our understanding of a phenomenon always follows the pattern from simplicity to complexity. For instance, our understanding of innovation system is from linear system, non-linear system and finally to complex system. Our need to understand the more complex system is a result of the growth in human knowledge, so we created more sophisticated tools enabling us to ask and answer questions about the complex world (Wilensky and Rand 2015).

The agent-based modeling is a method to investigate the complex adaptive system. An 'agent' is an autonomous computational individual or object with particular properties and behavior, and agent-based modeling is a kind of computational modeling whereby a social or natural phenomenon is modeled in terms of agents and their actions. ABMs are a powerful technique for simulating the complex adaptive system with the features of 'dynamics' and 'emergence'. There is currently a growing interest in developing ABMs as a method applicable to the study of the large-scale system. The agent-based modeling provides a unique potential for the research of innovation system. The potential has only been partially explored, but there are still many new and promising areas to investigate.

Recently, an increasing number of modeling toolkits have become available to facilitate ABMs, like Swarm, NetLogo, Repast, and MASON. In this research, the model was firstly built based on the software Swarm, which is the earliest and most stable toolkit for Multi-Agent Based Simulation. It uses both JAVA and Objective C as the programming language, and Objective C was applied to

program the model in this research. For the first basic model, Swarm was able to complete all the tasks except the difficulties in installation and very few supports from the community. But, when it was extended further by applying Genetic Algorithms to model the drug R&D process and the networks of the collaboration, the software showed its disadvantages: on one hand, the computational program (Java) became very complicated; on the other hand, the running speed was very low. Moreover, SWARM is weak in its ability to graph, which influences the results of further analysis. Although Swarm is still used by some experts, it has become outdated (Robertson 2005). Overall, Swarm's modeling functions cannot meet the requirements of the model we expect to build.

Table 14 The Comparison between NetLogo and Swarm

	NetLogo	Swarm
Date of Inception	1999	1996
Installation & Operation	Easy to set up and run	Difficult to set up and run
Programming experience	Basic	Strong
Active Maintenance	High	Low
Support from community	High	Relatively low
Model examples	Many	Only a few
Interface	Well-developed interface; parameters can be easily changed	Non-friendly interface
Additional features	3D visualization; Model can be embedded in web pages	Viable option for new modelers; Complex modeling structure

The second model is built by NetLogo, which is developed by Centre for Connected Learning and Computer-Based Modeling of Northwestern University. Like Swarm, NetLogo provides an integrated library of classes for creating, running, displaying and collecting data from the ABMs. Extensive user guides, tutorials and demonstration models are available from the system website, and the toolkit has been continuously updated since its inception. In addition,

NetLogo model is written in its own programming language. Compared with SWARM, NetLogo shows the advantages of the simple and clear structure, fast speed and especially the ability to model the complex adaptive system. Furthermore, NetLogo provides more powerful display tools (2D and 3D) that help users to do the thorough analysis. Finally, because users can develop the model without learning any comprehensive programming language, it is quite a recommendable toolkit for social scientists with insufficient knowledge of programming. In all, NetLogo is a 'low-threshold' and 'high ceiling' ABST, and it is able to build the complex adaptive model.

Chapter 6 Modeling Organizational Learning

6.1 Introduction

In the field of rapid science and technology development, organizations have to perform considerable adaption process to achieve successful innovation. They can change their innovation output incrementally by exploitation or radically through exploration. In most cases, organizations exhibit a mixture of both learning paradigms. The company should reach an appropriate equilibrium between the exploitation and exploration; otherwise, it may end up suffering from sub-optimization. For instance, if the company invests too much on exploiting old knowledge, it may lose its competitive advantage among its competitors.

In this chapter, we first recall the concept of the organizational learning and summarize the characteristics of it. Subsequently, the model of 'organizational learning' is articulated through Genetic Algorithms (GAs), and the characteristics of organizational learning activities are simulated and experimented. The differences and relationships between exploration and exploitation at the level of intra-organizational learning and inter-organizational learning are then discussed. Based on the modeling of organizational learning, lastly, a summary of this chapter is given.

6.2 Modeling Knowledge and Organizational Learning

As the firm is a body of knowledge (Nelson and Winter 1982), the knowledge-based theory of the firm offers a platform for considering the company as a dynamic, evolving, quasi-autonomous system of knowledge production and application. For instance, the pharmaceutical industry is a knowledge-based

industry, and knowledge can be considered as the critical dynamic capability of a company and the principal driver of all other competencies.

In biopharmaceutical sector, from the generation of a new idea to the marketing of a new product, the exploration and exploitation of knowledge is the driver of the new product innovation process (Rothaermel and Deeds 2004). The entire product innovation process can be regarded as a process of incorporating new knowledge into a product (Madhavan and Grover 1998). To get a more comprehensive understanding of the relationship between the knowledge and drug innovation process, we need to consider the paradigm of learning embedded into the product during the various stage of the drug innovation process.

Different stages of S&T development and different types of companies imply different paradigms of learning. In this section, the research employs March's exploration-exploitation framework to characterize the paradigm of learning, then to model different paradigms and compare the results.

6.2.1 Knowledge and Organizational Learning

The organizational learning is a routine-based, history dependent and target-oriented process; within this framework, organizational learning can be considered as encoding inferences from the history into routines that guide behavior (Levitt and March 1988). The 'routines' include the rules, procedures, strategies, and technology, all of which are the basis of organization construction and operation. Knowledge is stored in their routines, and organizations accumulate knowledge over time (March 1991).

Learning occurs through two primary mechanisms: trial-and-error experimentation and organizational search (incremental search) (Levitt and March 1988). The trial-and-error learning is a process by which the propensity to use specific routines is dependent on the history of outcome associated with

previous uses (March 2006). The organizational search takes place by drawing from a collection of alternative knowledge and adopting the better one, since the more successful ones are more likely to survive, grow and reproduce than the less successful ones.

This section is organized into three parts. First, the account is given of two learning processes: exploitation and exploration. Then, attention is given to the intra- and inter- organizational learning processes. The last part will be integrated by linking exploitation and exploration to intra- and inter-organizational learning.

6.2.1.1 Exploitation and Exploration

Learning is an important way to adaptively improve organizational performance and strengthen competitive advantage. The adaptive intelligence of organization can be divided into two activities, exploration and exploitation. The outcome of exploitation is predictable, while the outcome of exploration is much more uncertain (Powell, Koput et al. 1996). If the organization only engages in exploration, it will possibly never discover the useful knowledge, and the organization that engages exclusively in the exploitation will trap itself in the situation of 'suboptimal equilibrium' (Cohen and Levinthal 1989). Organizations should engage in both exploitation and exploration to sustain current viability as well as develop the future competitive advantage.

Exploration is a risky, costly process but the return of it is negative, uncertain and distant; while exploitation is a stable and inexpensive process, and the returns of exploitation are more positive, predictable and close (March 1991). Exploration can be considered as the innovation capability of the company by creating new knowledge, while exploitation is to improve or develop the current knowledge. The process of exploitation that is dependent on incremental learning is in a continuous way; in contrast, the exploration that is dependent on radical learning follows a discontinuous way. Both occur simultaneously during the process of organizational learning. In reality, most

companies engage in both learning activities simultaneously because once potentially valuable knowledge has been gained through exploration, the firm tries to exploit them further. The exploration-exploitation model implies a sequence for the use of this process by organizations (Rothaermel and Deeds 2004).

Both exploration and exploitation are essential components in organizational learning and are critical for an organization's competency. However, organizations should make choices in allocating resources between exploration and exploitation; the choice is affected by their distributed costs, benefits and ecological interactions (March 1991).

An exploration-exploitation model of organizational learning built by March (1991) explored the relations of exploration and exploitation in organizational learning and examined how to allocate resources between them. The way of development and diffusion of the organizational knowledge are modeled as individuals learn continuously from organizational knowledge while organizational knowledge is adapting to individual's knowledge. The improvement in the knowledge of individual and organization comes by mimicking mutually.

6.2.1.2 Intra-organizational learning and inter-organizational learning

There are another two concepts characterizing the organizational learning: one focuses on intra-organizational learning process and another one focuses on inter-organizational learning process.

Intra-organizational learning refers to that the new knowledge is created and developed within the boundaries of the firm; inter-organizational learning refers to that knowledge is transferred from outside sources through collaboration and acquisition. The intra- and inter- organizational learning are mutually interdependent and complementary processes. On one hand, companies should develop their absorptive capacity through internal learning

for better learning from outside; on the other hand, the process of intra-organizational learning can be accelerated and improved by effective inter-organizational learning.

The collaboration partners are the organizations that are different regarding the knowledge. and they bring a variety of knowledge to the collaboration. However, learning between organizations is not just imitating what they do not have, rather than absorbing and adapting the knowledge of their partners. They need to translate and integrate the knowledge into their existing knowledge base, and new knowledge grows out in the process of social interaction. Collaboration is an important source of knowledge creation. The more connections a organization has, the higher the diversity of its partner, the more likely it will generate new knowledge (Powell, Koput et al. 1996). When the knowledge base of an industry is complex and expanding, and the knowledge are dispersed, such as in the bio-pharmaceutical industry the locus of innovation is found within the inter-organizational networks.

6.2.1.3 The Synthesis of Organizational Learning Paradigms

The organization creates variety by exploration and reliability by exploitation; both of them must be applied together to accomplish a successful innovation. Exploitation and exploration take place both within and between organizations, and they interact through intra- and inter- organizational learning process (Holmqvist 2003). Exploration and exploitation can occur simultaneously within an organization or through interactions between organizations. In the first instance, the organization exploits and explores its knowledge base to find the best solution; in the second case, the organization exploits and explores its own knowledge base, but also obtains complementary knowledge from other organizations.

Within the organization, exploration takes place if the organization chooses to open itself to new resources, like the recruitment of new personnel, application

of new knowledge, or the employment of new equipment. Between the organizations, exploration is about seeking new partners that have the complementary competence. The intra-organizational learning is the essential part of inter-organizational learning process because what can be learned from inter-organizational learning lies in the confrontation and combination of organization's own knowledge (Holmqvist 2003). A single organization, by exploiting its own knowledge base, is able to create friendly conditions for the exploration that takes place within and between organizations.

Intra-organizational learning favors exploitation while inter-organizational learning favors exploration (Holmqvist 2003). This is because the higher extent of the stable environment, centralized coordination mechanism, and formal authority makes intra-organizational learning more stable and less innovative. Compared with the learning within a single organization, collaborations not only give the potential to share different knowledge among learning entities but also facilitate the creation of new knowledge.

Intra- and inter- organizational learning do not occur separately but are integrated into the learning process through the transformations of exploration and exploitation. A model built by Holmqvist (2003) describes the dynamics between learning process within and between organizations. The transformations between exploitation and exploration are 'opening-up' and 'focusing'. 'Opening-up' depicts a transformation from an ongoing process of exploitation to an ongoing process of exploration; it indicates that organizations choose to open itself up to the external knowledge. 'Opening-up' avoids suffering from obsolescence resulting from engaging exclusively in exploitation. After 'opening up', organizations discard obsolete and misleading knowledge from a variety of knowledge imported into the organization by exploration. 'Focusing' depicts a transformation from an ongoing process of exploration to an ongoing process of exploitation. The intra- and inter- organizational learning are integrated through four types of transformations (Holmqvist 2003).

- Exploitative extension occurs as a transition of exploitation inside the organization to exploitation between organizations. Through exploitative extension, organizations extend their knowledge and enable their knowledge to be exploited by their partners.
- Exploitative internalization takes place as a transition of exploitation between organizations to exploitation inside the individual organization. After exploiting partners' knowledge, organizations should refine and incorporate the knowledge they get into its own knowledge base.
- Explorative extension occurs as a transition of exploration inside the organization to between organizations. Through collaboration, organizations are able to get access to their partners' knowledge and create new knowledge with their partners.
- Explorative internalization takes place as a transition of exploration between organizations to exploration inside the single organization. Through explorative internalization, organizations internalize what they jointly explore with other organizations.

From the above, we can see the innovation is a process of knowledge creation driven by organizational learning, which is a dynamic process involving the intra-organizational learning process of exploitation and exploration as well as the inter-organizational learning process of exploitation and exploration. In this research, the dynamic learning process was simulated by the multi-agent Based Modeling.

6.2.2 Modeling

Many important insights in the organizational learning are based on simulations; for instance, March's studies on balancing exploration and exploitation in organizational learning are based on the agent-based model (ABM). The ABM is also widely used in the organizational and adaptive learning research.

Our simulation model is built as an ABM to simulate the organizational behavior. It integrates the Genetic Algorithms (GAs) to simulate organizational learning activities. In the ABM, the organization is represented by the agent with a high degree of heterogeneity and bounded-rational. Because ABM is path-dependency, the agents' behaviors rely on their history. The agents are modeled as isolated or connected with other agents. Moreover, they have different behavioral rules, so they can show different learning paradigms. As the agents are bounded rational, they can accumulate the ability of learning (R&D) based on the learning from past experience.

6.2.2.1 Genetic Algorithms

Since GAs have drawn analogies from biology (Table 15) to solve an optimization problem, GAs start with the chromosomal representation of a parameter set. The set is coded as a finite-length binary string, and each binary string represents selected characteristics of one of the candidates in the population. Search space refers to the collection of possible solutions to the problems.

Table 15 The Mapping of Biology, Genetic Algorithms and Organizational learning

Biology	Genetic Algorithms	Organizational Learning
Gene	Bits	Specific knowledge
Chromosome	Binary String	Knowledge
Population	Search Space	Collection of knowledge
Evaluation function	Fitness function	Fitness of learning
Selection	Selection	Exploitation
Reproduction	Crossover	Exploration (Innovation)
	Mutation	

The Genetic Algorithm applied in our model is an abstract model of the evolution with a fixed population of individuals represented by fixed-length 'genetic' strings. The simple GAs are designed as simulation tools for

phenomena characterized as complex, non-linear and emergent behavior, rather than for solving a particular problem. The key point of the GAs is the adaptation process by making new individuals using genetic operators rather than making incremental changes to a single individual, and GAs are best viewed as the design tool for the learning system (De Jong 1988). In the learning model, the environment defines one or more tasks, and the learning process includes the skill acquisition and refinement. The learning model of GAs can be visualized as a system consisting two components: the task system whose performance is affected over time by learning, and a learning system responsible for controlling the performance of task towards the desired objective (De Jong 1988).

6.2.2.2 Translate Organizational Learning into Genetic Algorithms

The research about the organizational learning has addressed the question of the location of learning and explained that it could take place at the individual and organizational level (Bapuji and Crossan 2004). In our model, the organizational learning is modeled at the organizational level, which not only includes the intra-organizational level but the inter-organizational level. The learning at the organizational level doesn't mean an organization is capable of learning since the learning is not an inherent property of an organization, rather than individuals learn on behalf of the organization.

Knowledge

In the model, the genetic algorithm begins with a group of chromosomes known as population, which is a collection of knowledge. Each chromosome means a piece of knowledge in the learning process. In most cases, at the beginning of the simulation, knowledge is generated randomly based on initial condition.

In this model, at the beginning of the simulation, each organization is initialized with a collection of knowledge. The collection is a $N_k \times N_{bit}$ matrix that has N_k pieces of knowledge, and every piece of knowledge is filled with N_{bit} ones or

zeros randomly based on the initial condition. Every piece of knowledge, represented as a binary string contains $N_{bit} = 100$ binary codes (0 or 1), is linked to a fitness value. In our model, the fitness is calculated as the proportion of the number of correct/qualified digits $bit_i=1$:

$$F = \frac{1}{N_k} \sum_{i=0}^{N_k} \left(\sum_{i=0}^{N_{bit}} bit_i \right) \quad (1)$$

Each organization has an initial knowledge base, which is codified through a collection of random binary strings based on the initial condition. The initial condition is:

- 1) each origination has $N_k = 20$ (narrow knowledge base) or $N_k = 40$ pieces of knowledge (broad knowledge base);
- 2) each piece of knowledge has $N_{bit} = 100$ binary codes;
- 3) the initial fitness value of each piece of knowledge is $0 \leq F \leq 20$.

The population size is constant, which means although the reproduction results in the new offspring the selection process is invoked to reduce the population size back to N_k . In each simulation time-step, the fitness of knowledge collection is evaluated according to its contribution to the drug discovery.

Organizational Learning Process

For the learning process, ABMs in economics apply mathematical methods such as GAs (Kauffman 1993, Riechmann 1999). The exploitation is modeled by the selection through GAs. In each period, organizations choose the knowledge from its knowledge base with the high value of F . With respect to exploration, an organization continuously improves its knowledge base by generating new knowledge. The learning process is implemented by the GAs operators: crossover and mutation. To begin with, the knowledge undergoes the crossover process with a probability P_c (crossover rate), in a randomly selected crossing-over point. Following the crossover, each binary code mutates (the binary code

flips into its opposite, from 1 to 0 or from 0 to 1) with a probability P_m (mutation rate).

Exploitation

The chromosomes are selected from the old generation for crossover and mutation based on their fitness value. Usually, the higher fitness a chromosome has, the more likely it will be selected to reproduce. Effective selection methods should ensure that the best chromosomes are selected. However, according to the evolutionary economics, the economic agents are heterogeneous and bounded-rational. For instance, in the pharmaceutical industry, at the beginning of drug discovery process organizations do not have a clear idea about what a successful drug candidate should be. Organizations are not able to select all the useful knowledge with bounded ration.

Tournament selection is used to model the exploitative learning process. Tournament selection is a selecting method involving running several tournaments among a few individuals chosen randomly from the population, and the winner of each tournament (the one with the best fitness) is selected. In the model, three pieces of knowledge are drawn randomly from the knowledge collection, and the one with the highest fitness is selected to become a parent to reproduce. The efficiency of selection is determined by the tournament size. The larger the tournament size, the smaller the chance the weak individual is selected. Accordingly, the selection is modeled as 'tournament selection' with a tournament size of 3.

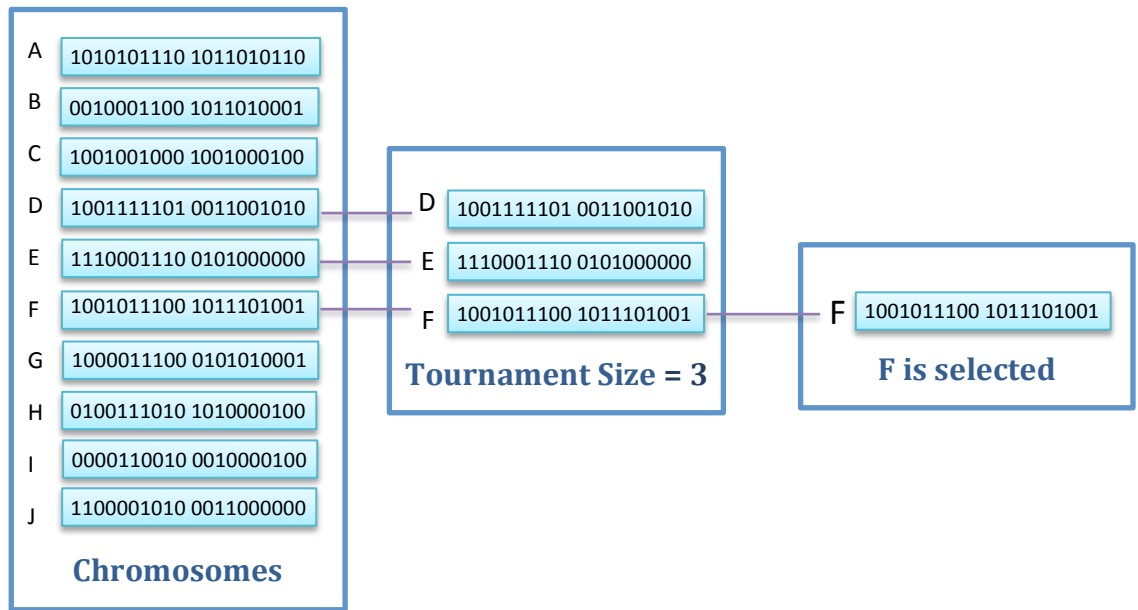


Figure 27 The process of Tournament Selection

The mechanism of tournament selection is shown in Figure 27. We assume that there are 10 chromosomes (from A to J) in the population. Because the tournament size is 3, in each time-step 3 chromosomes are chosen randomly from the population (D, E, F). In Table 16, F is the chromosome with the highest fitness value among D, E, and F, so chromosome F is selected.

Table 16 The Fitness Value of Chromosomes

Item	A	B	C	D	E	F	G	H	I	J
Fitness	12	7	6	10	8	11	8	7	5	6

Exploration

The crossover operator has been considered as the most distinguishing feature of the GAs (Davis 1991). The idea behind crossover is that the new generation is likely to be better than their parents by recombining the best characteristics from both parents.

Mutation is an important genetic operator that alters one or more bits of gene values in the chromosome. This operation can result in the entirely new chromosome, with which the GAs can arrive at the better solution. The objective of the mutation is to maintain the diversity within the population and inhibit premature convergence.

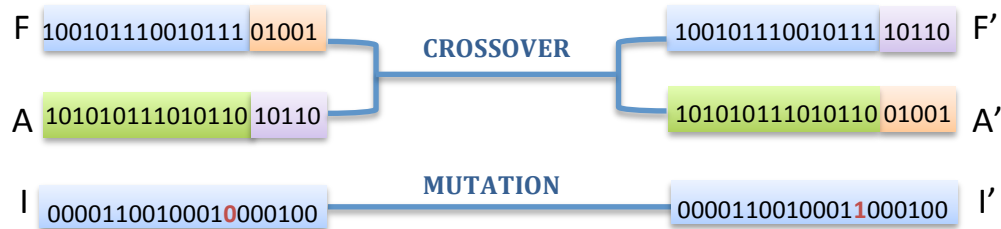


Figure 28 The Way of Crossover and Mutation

The mechanisms of crossover and mutation are shown in Figure 28. Two chromosomes (F and A) are randomly selected from the collection to crossover based on probability P_c (crossover rate), and the last five binary codes are exchanged between F and A. After the crossover, two new chromosomes F' and A' are created. A binary code in the chromosome (I) is randomly selected to mutate based on probability P_m (mutation rate), the 14th binary code is switched from 0 to 1. Compared with I', although F' and A' are different from F and A, and nothing new is brought into the collection in terms of the binary code in each position.

Parameter Setting

The effects of different genetic operators are different. If there is only selection in the GAs, the new generation is always the copies of best individuals from the population. Therefore, selection can improve the performance of the drug discovery but only in the short term, without creating new knowledge the organization will fall into a learning trap. Using selection and crossover will lead to the GAs to converge on a good but not the best solution. If only using mutation, the algorithms are similar to the random walk through the search space. Combining the selection and mutation, the GAs are similar to the hill climbing algorithms that start at an arbitrary solution and then try to improve

the solution by incrementally changing a single element of the solution (if the solution is better, the change is made to the new solution; if the solution is worse, the original solution is retained).

The values of population, crossover rate, and mutation rate have a significant influence on the performance of genetic algorithms. That means we can use different settings of GAs' operators to show the differences of drug discovery processes. De Jong has performed a systematic study of how varying parameters influence the GAs performance. The experiments have shown that the best population size is 50-100, the best single-crossover rate is 60%, and the best mutation rate is 0.1% (De Jong 1988).

In our model, the genetic algorithm is used to show the organizational learning process rather than to find the solution as fast and correct as possible, which is different from the traditional applications of GAs. Therefore, the parameter setting in this model is different from De Jong's setting. In order to show the different level of learning ability, the crossover rate is set as:

$$P_c \in (0.2\%, 0.4\%) \quad (2)$$

The setting of mutation rate characterizes the degree of exploration. According to the research, the mutation rate is usually set between 0.05% and 1% in the GAs (Srinivas and Patnaik 1994). Therefore, the mutation rate in this model is set in this range to show the different level of exploration in the organizational learning process.

$$P_m \in (0.05\%, 0.5\%) \quad (3)$$

When mutation rates are set too large ($P_m > 1\%$), the whole genetic algorithm is transformed into a random search algorithm, because the spontaneous change rates undermine the continuous improvement process (De Jong 1988, Srinivas and Patnaik 1994). Accordingly, in the model, the mutation rate is set at the

value bigger than 1% to show the random-search learning paradigm, which will be used to model the random screening of drug discovery.

6.3 Modelling Results

Through the tournament selection method, the knowledge base is refined through the process of exploitation. Alternatively, the organization can create the knowledge that is new to the existing knowledge base. The learning process can be considered as the explorative learning. Compared with exploitation, which refines the knowledge base without creating any new knowledge, the exploration process changes the knowledge base by bringing in new knowledge, which is distinct from the knowledge into the existing knowledge base. Therefore, the organizations in our model are divided into three types according to the degree of exploration, medium degree (M), high degree (H) and very high degree (V).

The simulation analyzes the organizational learning in three experiments. Both the isolated performance of exploration and exploitation or the combination of them is simulated. In terms of the isolated paradigms, as shown in Table 17, **Experiment 1** has six settings: 1) the intra-organization exploitation (INTRA-ET-0); 2) the intra-organization exploration with the medium level of innovation (INTRA-ER-M); 3) the intra-organization exploration with the high level of innovation (INTRA-ER-H); 4) the inter-organization exploitation (INTER-ET-0-M); 5) the inter-organization exploration with the medium level of innovation (INTER-ER-M-M); 6) the inter-organization exploration with the high level of innovation (INTER-ER-H-M).

Table 17 The Simulation Settings of Experiment 1

Experiment 1					
Learning Locus	Number	Learning Paradigm	Level of Innovation	Network Density	Abbreviation
Intra-Organizational Learning	Org 1	Exploitation	-	0	INTRA-ET-0
	Org 2	Exploration	Medium	0	INTRA-ER-M
	Org 3	Exploration	High	0	INTRA-ER-H
Inter-Organizational Learning	Org 4	Exploitation	-	Medium	INTER-ET-0-M
	Org 5	Exploration	Medium	Medium	INTER-ER-M-M
	Org 6	Exploration	High	Medium	INTER-ER-H-M

In addition to the above six settings, *Experiment 2* (Table 18) analyzes the intra-organizational learning with the combination of exploration and exploitation: 7) the intra-organization exploitation and exploration with the medium level of innovation (INTRA-BT-M); 8) the intra-organization exploitation and exploration with the high level of innovation (INTRA-BT-H); 9) the intra-organization exploitation and exploration with the very high level of innovation (INTRA-BT-V).

Table 18 The Simulation Settings of Experiment 2

Experiment 2					
Learning Locus	Number	Learning Paradigm	Level of Innovation	Network Density	Abbreviation
Intra-Organizational Learning	Org 7	Both	Medium	0	INTRA-BT-M
	Org 8	Both	High	0	INTRA-BT-H
	Org 9	Both	Very High	0	INTRA-BT-V

In *Experiment 3* (Table 19), four settings are simulated to examine the inter-organizational learning with different level of innovation and network density: 10) the inter-organizational exploitation and exploration with the medium level of innovation and medium network density (INTER-BT-M-M); 11) the inter-organizational exploitation and exploration with the high level of innovation

and medium network density (INTER-BT-H-M); 12) the inter-organizational exploitation and exploration with the medium level of innovation and high network density (INTER-BT-M-H); 13) the inter-organizational exploitation and exploration with the high level of innovation and high network density (INTER-BT-H-H).

Table 19 The Simulation Settings of Experiment 3

Experiment 3					
Learning Locus	Number	Learning Paradigm	Level of Innovation	Network Density	Abbreviation
Inter-Organization Learning	Org 10	Both	Medium	Medium	INTER-BT-M-M
	Org 11	Both	High	Medium	INTER-BT-H-M
	Org 12	Both	Medium	High	INTER-BT-M-H
	Org 13	Both	High	High	INTER-BT-H-H

In order to prevent results with artifacts of idiosyncratic values, the knowledge base of the organization is created randomly at the start of the simulation. Moreover, the following simulation results show the average performance of the organization over time. Aimed at obtaining a reasonable statistical analysis, the following results are based on 10 simulation runs, each lasting 100 periods.

All the organizational learning tasks are assumed with the same difficulty. At the beginning of the simulation, the fitness values of the knowledge base are set at 20. Based on this assumption, we can compare the different performance of the organization with varying learning paradigms.

6.3.1 Experiment 1: Learning with either Exploration or Exploitation

The information in Table 20 shows the organization's learning performance in the first and last period of the simulation. At the beginning, organizations with different learning paradigms have the same knowledge base, but different

learning paradigms lead to different learning performances.

Table 20 The Result of Experiment 1 & 1'

The Breadth of Knowledge Base	Organization	First period	Last period	Period (F>=80)
Narrow	INTRA-ET-0	20.300	27.000	-
	INTRA-ER-M	20.150	36.364	-
	INTRA-ER-H	20.200	67.409	-
	INTER-ET-0-M	20.100	78.000	-
	INTER-ER-M-M	20.200	55.955	-
	INTER-ER-H-M	19.900	75.455	-
Broad	INTRA-ET-0'	20.075	29.000	-
	INTRA-ER-M'	19.825	41.727	-
	INTRA-ER-H'	20.025	67.955	-
	INTER-ET-0-M'	20.125	85.000	89
	INTER-ER-M-M'	20.000	49.114	-
	INTER-ER-H-M'	19.950	73.432	-

**INTRA and INTER indicates the locus of learning: intra-organization or inter-organization; ET, ER and BT indicates the ways of learning: organizations learn by exploitation or exploration or both of them; M, H, and V refers to medium high and very high level of exploration, 0 indicates no exploration in the organizational learning; ' indicates organizations learn with broad knowledge base, otherwise, organization learns with narrow knowledge base.*

Experiment 1&1' is simulated to exhibit the influence of the breadth of the knowledge base. In Experiment 1, the knowledge base is narrow since there are 20 units in the knowledge collection, while the knowledge base is enlarged to 40 units in each knowledge collection in Experiment 1'.

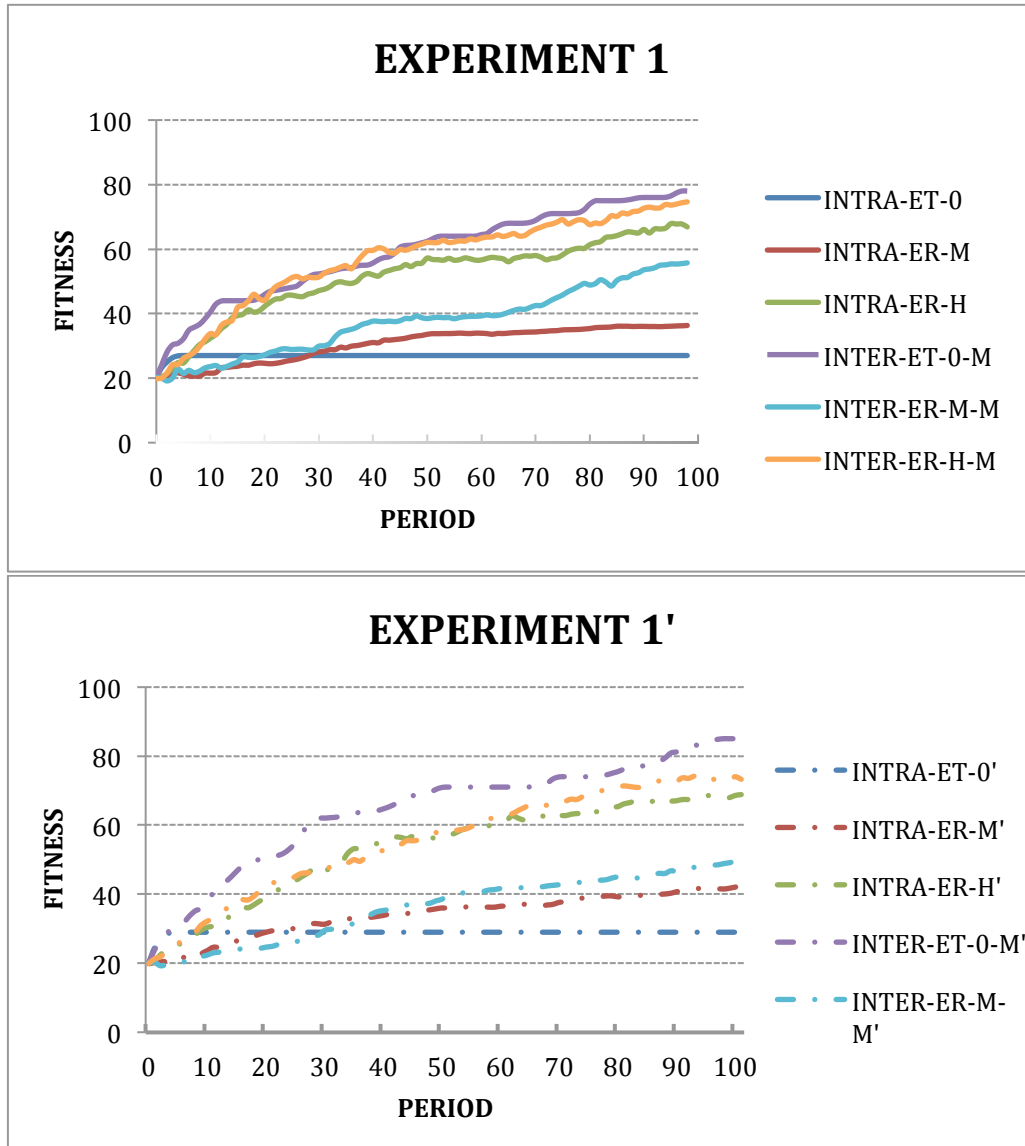


Figure 29 The Result of Experiment 1 & 1'

Exploitation

In Figure 29, intra-organizational exploitation (INTRA-ET-0, solid blue line) shows very little improvement of the knowledge. Overall, it shows the worst performance in all six settings. Intra-organizational exploitation focuses on the refining of existing knowledge within an organization. Hence, this learning paradigm only offers the possibility to improve the learning by selecting the good knowledge in the knowledge base. The fitness value of the knowledge increases steadily during the first several time-steps, and then the fitness value

keeps at the same level. Moreover, in the six settings, this restriction is even not solved out through the enlargement of the organizations' knowledge bases (INTRA-ET-0' blue dash-dot line).

Exploration

The uneven lines of intra-organizational and inter-organizational exploration show the random trials of exploration. The organization learning with exploration exhibits a better outcome than the organization learning with exploitation; and the performance of intra-organizational learning with the high level of innovation (INTRA-ER-H, solid green line) is better than the performance of intra-organizational learning with the medium level of innovation (INTRA-ER-M, red solid line).

Network

In all the six settings, the configurations of intra-organization learning exhibit a lower rate of improvement than inter-organization learning. Inter-organizational exploitation (INTER-ET-0-M, solid purple line) offers the possibility to obtain useful knowledge from other's knowledge bases. Therefore, in contrast to intra-organizational exploitation, the more extensive space of possible solutions can be more efficiently searched in the inter-organizational exploitation, and it exhibits the best performance in Experiment 1 and 1'.

The inter-organizational exploration is more effective than intra-organizational exploration, as the new knowledge can be acquired through the network to enrich the knowledge base. The inter-organizational exploration with the medium level of innovation and the medium level of network density (INTER-ER-M-M) doesn't show the advantage compared with intra-organizational learning with the high level of innovation (INTRA-ER-H). This indicates the network can improve the organization's learning performance, but the organization's own ability of learning is also very important. All the four configurations of inter-organizational exploration (INTER-ER-M-M, INTER-ER-M-H, INTER-H-M, INTER-ER-M-M', INTER-M-H') display a lower level of

improvement than the inter-organizational exploitation (INTER-ET-0-M, INTER-ET-0-M'). It implies although exploitation is not as effective as exploration in the intra-organizational learning, the network is more critical for the organization learning with exploitation than learning with exploration.

Knowledgebase

From the comparison of *Experiment 1* and *1'*, increasing the width of knowledge base has a positive influence on the final performance level of all the learning configurations.

6.3.2 Experiment 2: Learning with both Exploitation and Exploration

Experiments 1 and 1' show the learning performance with either exploitation or exploration. Experiments 2 and 2' examine the learning performance with both exploitation and exploration.

The performances of organizational learning with both exploration and exploitation in the first and last period of the simulation are shown in Table 21. Regarding the breadth of knowledge, Experiment 2' shows the different performances of organizational learning when the organizations have the broader knowledge base. From Experiments 1 and 1', it is evident that the higher the level of exploration, the better the outcomes of innovation an organization can achieve. However, when the mutation rate is set at a high level (V), it will influence the outcome of learning by bringing great uncertainty. When the mutation rate is set at 5% (INTRA-BT-V or V'), the curve of learning performance is less smooth than when the mutation rate is set at 0.05% (INTRA-BT-M or M') or 0.1% (INTRA-BT-H or H'). The rough curve indicates the random-search feature of trial-and-error learning.

Table 21 The Result of Experiment 2 & 2'

The Breadth of Knowledge Base	Organization	First period	Last period	Period (F>=80)
Narrow	INTRA-BT-M	20.300	58.864	-
	INTRA-BT-H	20.150	94.136	49
	INTRA-BT-V	20.200	76.227	-
Broad	INTRA-BT-M'	20.075	65.205	-
	INTRA-BT-H'	19.825	94.522	46
	INTRA-BT-V'	20.025	78.250	-

Figure 30 depicts the different processes of the organizational learning with different levels of exploration and width of knowledge base over time. The result indicates that a broad knowledge base leads to a successful innovation at a faster speed.

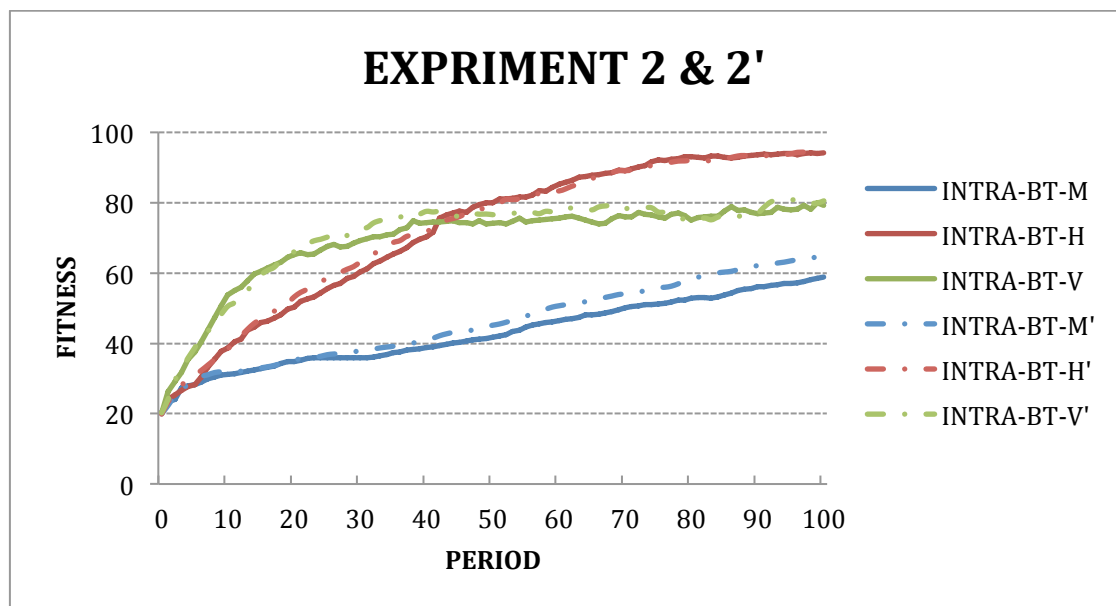


Figure 30 The Result of Experiment 2 & 2'

6.3.3 Experiment 3: Learning in the network

Experiments 1 and 2 show that organizations doing both exploitation and exploration perform better than organization engaged in only doing exploitation or exploration. In addition, inter-organizational learning has better outcomes than intra-organizational learning. In experiment 3, we examine the influence of network density on inter-organizational learning performance.

Table 22 provides the information on the performance of eight configurations of the inter-organizational exploration and exploitation. The broader knowledge base brings less advantage to organizational learning, comparing Experiments 1 & 1' and 2 & 2'. The most important reason is that organizations can access a variety of knowledge through relationships with its collaborators.

Table 22 The Result of Experiment 3 & 3'

The Breadth of Knowledge Base	Organization	First period	Last period	Period (F>=80)
Narrow	INTER-BT-M-M	20.300	88.955	64
	INTER-BT-H-M	20.150	94.182	46
	INTRE-BT-M-H	20.200	92.000	56
	INTRE-BT-H-H	20.200	96.636	33
Broad	INTER-BT-M-M'	20.300	91.978	69
	INTER-BT-H-M'	20.150	96.659	41
	INTRE-BT-M-H'	20.200	96.655	51
	INTRE-BT-H-H'	20.200	96.887	32

Figure 31 depicts different inter-organizational learning processes over time. The result illustrates that organizations with a high level of exploration and network density learn differently compared with the organizations with lower levels of exploration and network density. As shown in *Experiments 3 and 3'*, they outperform organizations with little innovativeness and low network

density. For the same level of network density, a higher level of exploration leads to a better performance of the organization; and for the same level of exploration, a higher value of network density engenders a better outcome from the innovation. Hence, organizations with high innovativeness and network density perform the best.

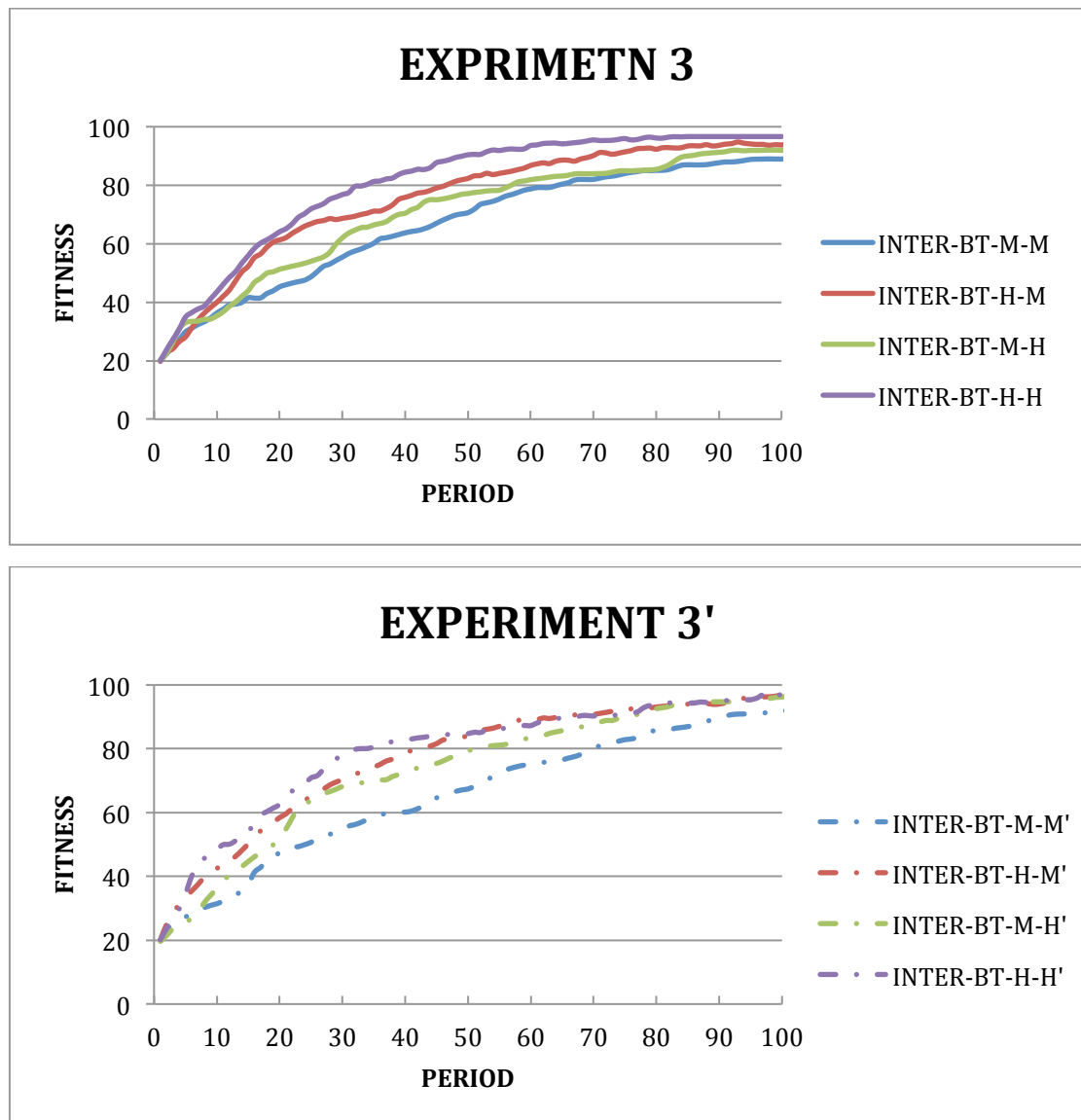


Figure 31 The Result of Experiment 3 & 3'

6.3.4 Discussions

The results of the simulation are based on the abstract model of the organizational learning process. The above simulation experiments examined the influence of the different ways of handling knowledge on the innovation outcomes. These results have provided several implications for future research regarding the organizational learning.

Firstly, the results of *Experiment 1* have shown the different evolution processes of the organizational learning through either exploitation or exploration. Exploitation is about creating reliability from the experience, and it includes activities like refining their abilities, developing their existing knowledge, learning on specific domains and from successful or failed experience (Holmqvist 2003). From comparing the case of INTRA-ET-0 and INTRA-ET-0', we can find that firms that keep exploiting their existing knowledge tend to fail. This is because the positive local feedback can produce strong path dependence and lead to suboptimal equilibrium. Therefore, it is entirely possible for organizations only using exploitation in their R&D to achieve less optimal R&D outcomes. The wide range of knowledge base seems likely to increase the reliability, the effect of which is to avoid the organization being the worst one rather than ensuring that the organization is the first one.

As the long-term intelligence is dependent on maintaining an appropriate level of exploration, strategies that involve a high level of exploitation, a very low level of exploration or without exploration make the adaptive learning process self-destructive. The research summarized three different learning traps that organizations may fall into: organizations may fall into the familiarity trap because they intend to use known solutions (INTRA-ET-0); they may fall into the maturity trap due to aptly proven solutions; and organizations may fall into the propinquity trap because of tendency to use solutions closer to known solutions (INTRA-BT-M) (Ahuja 2000). The strategy with a medium and high level of exploration leads to better outcomes than the strategy with only

exploitation. Exploration is the source of innovation in the organizational learning. It is believed that big companies are more exploitative while small companies are more explorative. As a result, smaller and younger firms are more likely to make important innovations than older and larger firms, such as biotechnology companies that are the main source of innovation in the biopharmaceutical industry.

In the dynamic environment, learning and gaining experience are very hard for organizations. Firm-specific factors influence the learning strategy, such as culture, strategy, structure, and environment (Bapuji and Crossan 2004). The exploitation and exploration can be understood as the similarity and diversity trade-off. Exploitation prospers from the similarity in previous knowledge; while exploration prospers from the diversity in new knowledge. In March's model, an organization's performance is characterized in terms of the measure of average value and variability of knowledge, moreover, only when learning increases the mean and the variance of the knowledge, it will improve the competitive advantage of the organization (March 1991). Most of the organizations employ the learning strategy with both exploitation and exploration to gain competitive advantage, but different organizations have different strategies for learning and therefore for deploying resources between exploitation and exploration. The attributes of the industry affect the learning strategy of companies, such as the companies in service industry pay more attention to exploitation compared with biopharmaceutical industry where companies pay more attention to exploration. The evolutionary stage of an organization also affects company's learning strategy. For instance, some biotechnology companies rely on other organizations for learning during their early stage of development but focus on internal learning as they mature (Oliver 2001).

Secondly, **Experiment 2** illustrates how the different settings of mutation rate influence the learning evolution process. According to the evolutionary theory, the variety results from sampling variation (the combinatorics of mating) and

arbitrary random error (mutation) (March 1996). Even the crossover rate is set at a high level, if the mutation rate is set at a very low level, the organization will suffer from the learning trap. Mutation is regarded as inexplicable or unpredictable random events. Both trial-and-error learning and organizational search are gradually adaptive processes that lead to desired outcomes (Levitt and March 1988). Hence, when the mutation rate is set at a very high level of 5% and above (INTRA-BT-V), the learning curve exhibits the characteristics of the uncertainty of random screening. The learning process is like a failure-induced search for optimization, so it can be considered as trial-and-error learning. When the mutation rate is set in the range between 0.05% and 0.1%, with the increase of mutation rate organizations are able to learn better. Since the increase of knowledge base is not sufficient to overcome the adverse effects produced by the reduction in variability (March 1991). With the increase of mutation rate, organizations can better adapt to the changing environment on the way to optimization (INTRA-BT-M and INTRA-BT-H).

The exploitation learning process contributes to an increase in the similar knowledge rather than the ability to find new opportunities. So, to overcome the disadvantages of exploitation, organizations should create variety by experiment and innovation. As Levin and March (1993) stated: “an organization that engages exclusively in exploitation will ordinarily suffer from obsolescence” while “an organization engages exclusively in exploration will ordinarily suffer from the fact that it never gains the returns of its knowledge.” The increase in exploitation or knowledge base is less effective than the increase in variability when the competition among organizations is severe. That indicates those organizations with limited resources are willing to sacrifice average performances in order to increase variety.

These dynamics have shown us that the best strategy for small biotechnology companies with limited resource and relatively narrow knowledge base is not to enlarge their knowledge base but to increase the variation of their knowledge in the first place. The issue of keeping an appropriate balance between

exploration and exploitation to achieve the optimum is a big challenge for the company.

Thirdly, the findings exhibit considerable differences between the intra- and inter-organizational learning paradigms with respect to the evolution and the final organization performance. From **Experiment 3**, we find that the inter-organizational learning improves the outcomes of learning efficiently. The intra-organizational learning paradigms stick to the organization's existing knowledge, while the inter-organizational learning paradigms depend on its cooperative partners to develop knowledge. Given the same intra-organization learning strategy, a relatively high level of network density leads to better performance. INTER-BT-M-H shows better innovation performance than INTER-BT-M-M, and INTER-BT-H-H is superior to INTER-BT-H-M. These results are consistent with the empirical findings (Powell, White et al. 2005).

Compared with the learning within a single organization, the learning between organizations is of a highly innovative and explorative characteristic since they share different knowledge between learning entities. Although inter-organizational learning enables the organization to enrich their knowledge stock with the knowledge previously unavailable within the organization, the ability of intra-organizational learning plays a significant role in the learning alliance. The result shows that the performance of INTER-BT-M-H is inferior to the performance of INTER-BT-H-M, which indicates that more cooperators are not able to make up the weak ability of intra-organizational learning.

The type of collaboration among companies and research organizations can be divided by its purpose. Company's decision on the cooperation can be differentiated regarding its desire to exploit an existing capability or to explore new opportunities. Different stages of product innovation process have different types of learning and thus drive drug companies to enter into different kinds of alliances. In biopharmaceutical sector exploration collaboration usually indicates that the drug R&D is in the discovery process and exploitation

collaboration usually indicates the drug R&D is in the development process. The exploration collaborations are built with the aim to discover something innovative, the organizations involved in exploration collaboration focus on generating new knowledge. In biopharmaceutical sector, exploration collaborations are motivated by the expectation for creating cutting-edge fundamental knowledge that can be applied to discover novel drug candidate (Rothaermel and Deeds 2004). An example of exploration collaboration is the alliance between research institutions and biotechnology companies during the drug discovery process. Exploitation alliances are characterized by the sharing of complementary assets; for instance, biotechnology companies collaborate with Big Pharma in the drug development stage with the aim to fill the knowledge gap in the clinical trial.

Organizations can learn more efficiently from its collaborators if they share the similarity in the knowledge base, organizational structure, and dominant logic. For instance, drug companies choose to cooperate with companies having the similar or related research area. Moreover, a firm's knowledge learned from its collaborators relies on its prior experience with that partner. Firms select their partners also on the basis of the collaborators' knowledge base and their inclination to share it. If two organizations have very similar knowledge base, there is no gain from inter-organizational learning, and if the organizations have the entirely different knowledge base, then it's likely impossible for the organizations to learn from each other.

Fourthly, according to the three experiments, the effective mechanism of the cycle of learning is discussed. The learning paradigm now takes account of exploitation/exploration and intra-/inter-organizational learning. The ability to redeploy existing knowledge is fundamental to long-term strategic advantages. First of all, what an organization knows at the beginning will influence its learning objective, learning experience and how it interprets what it experiences (Huber 1991). Therefore, the initial knowledge base strongly affects future learning, which includes both intra- and inter- organizational

learning. Generally, the higher rate of learning leads to achieve optimization earlier. The level of knowledge attained by an organization is also affected by different learning paradigms. **Experiment 1** shows the results when we assume that organization only learn by exploitation or exploration. The results have confirmed why most organizations engage in both exploitation and exploration. The results have been extended by examining organizational learning in a more open system, specifically, when the role of the inter-organizational learning is considered.

The learning occurs between organizations is not simply copy another organization's knowledge rather than the knowledge of former is varied by adapting its present knowledge. Knowledge cannot be simply transferred from one organization to another; it has to be translated and integrated into the existing knowledge base. The translation process is realized through the intra-organizational learning process. The previous success may not ensure the organization competent at the end, especially when the organization cannot effectively adapt to the changing environment. In a research about the pharmaceutical industry, drug companies that focus on not only incremental and radical learning, but also internal and external learning, were found to be more innovative than others (Bierly and Chakrabarti 1996).

6.4 Summary

All the learning configurations we simulated differ in the way knowledge is handled. Therefore, the classification of both exploration and exploitation at the intra-organization level and inter-organization level is an appropriate starting point for this research. The results of the simulation have indicated that the outcome of isolated explorative and exploitative learning at intra-organizational level is not efficient. Although the intra-organizational exploitation has the best outcome in experiment 1 & 1', the innovation outcome is still poor compared with the organization engaging in both exploration and exploitation. Hence, only

the integration of exploration and exploitation can foster organizational performance and lead to a better outcome. Moreover, the inter-organizational learning has shown better performance than intra-organizational learning through accessing complimentary knowledge, and the more organizations they collaborate with the bigger possibility that they achieve successful innovation.

In all, the intra-organizational and inter-organizational learning processes interact through the processes of exploitation and exploration. It is not hard for the organizations to be trapped in the innovation process. Organizations can avoid traps by employing exploitation and exploration as well as intra- and inter-organizational learning. Under different conditions, organizations develop their own ways to deploy resources between exploitation and exploration as well as inside learning and outside learning to gain the competitive advantage in the changing environment.

The organizational learning model we presented offers a better understanding of the different influences of exploitation/exploration and intra-/inter-organizational learning on the outcomes of innovation. It is a general learning model that can be further developed to analyze the innovation activity of a single organization or a cluster of organizations; moreover, it can be used to explain the dynamics and evolution of innovation system in different countries, regions, and industries. Therefore, based on the model presented in this chapter, in Chapter 7, the model of the innovation system of biopharmaceutical industry is built, and it's further applied to explore the influence of public intervention on the sectoral system of innovation.

Chapter 7 Modeling Orphan Drug Innovation

7.1 Introduction

In the last century, with significant changes to science and technology, pharmaceutical research has evolved from the pattern where random discoveries dominated drug discovery to a more rational and guided model (Quéré 2004). The traditional R&D of drugs is the ‘random screening’ through serendipity (Ratti and Trist 2001). The process is featured by extreme uncertainty due to lack of the knowledge about the causes of diseases and the mechanisms of the action of drugs. From the late 1970s, the advances of biotechnology have improved the knowledge about the mechanisms of diseases as well as the action of drugs. In turn, these advances contributed to an innovative way of drug R&D, from trial-and-error approaches to ‘rational drug design’ (Garavaglia, Malerba et al. 2010). After the 1990s, the external collaboration is common in the pharmaceutical industry in light of the need for companies to exploit and explore the complementary resources (Powell, Koput et al. 1996, Quéré 2004). The main objective of the alliance is to learn, transfer, adsorb and explore new knowledge. Hence, the drug discovery can be divided into three phases: ‘Before the 1980s’ - the random discovery phase, ‘The 1980s’ – the rational discovery phase; ‘After the 1990s’ – the network discovery phase.

This chapter is structured into two parts. In the first part, different periods of drug discovery are briefly reviewed. Specifically, we focus on the distinct learning patterns in each period and apply the model of organizational learning to simulate these diverse innovation activities. A Multi-Agent Based Model integrated with Genetic Algorithms is built to simulate the drug discovery in three periods: before the 1980s, the 1980s and after the 1990s.

The second part of this chapter is dedicated to the modeling of orphan drug innovation and exploring the influence of the ODA. The modeling in this part

leads us to the core idea of the thesis. Several empirical studies on the orphan drug innovation process are presented, based on that the multi-agent-based model is applied to investigate the influence of the ODA on orphan drug innovation and examine the controversies around the 7-year market exclusivity.

7.2 Modeling Drug Discovery

The rapid changes in science and technology drive organizations to pursue the goal of developing new products. Therefore, it is vital for the organizations to learn quickly and efficiently. In the last several decades, pharmaceutical research has evolved from a pattern where random screening dominated the drug discovery to a more rational and guided model.

The steps of the complicated drug discovery process can be divided into five major phases: target identification and validation, lead identification, lead optimization, and drug selection (Figure 32). The outcome (drug candidate) of this process cannot be sold directly on the market, because it must be tested based on its safety and effectiveness. Only the qualified drug candidate can pass the examination and get market authorization.



Figure 32 Drug Discovery Process

7.2.1 Different Periods of Drug Discovery

In terms of the pharmaceutical research, there are two ways for firms developing their local competencies. The first one is the firm-specific expertise in particular disciplinary areas and the second one is the expertise in particular

disease areas (Cockburn and Henderson 2001). Pharmaceutical companies focusing on different diseases may have their specific expertise. Modern drug discovery requires the input of the scientists skilled in a wide variety of disciplines. However, the area of disciplines has changed greatly since the 1970s.

The advances in biology and human genomics stimulated the new era of drug discovery, which can be considered as evolution (Tsinopoulos and McCarthy 2002). The strategy for drug discovery meets the four requirements of evolution. The first requirement of evolution requires a certain number of drug discovery strategies to form populations. The second one is variation, which is caused by both the disease and the discovery environment. Different organizations commit themselves to different therapeutic areas. For instance, some developers focusing on cardiovascular science while others concentrate on cancer. They often pursue unique strategies to achieve the competitive advantages. The environment factors include the knowledge and experience of the organization. The third requirement is heredity, based on which reproduction takes place via passing the knowledge from one step to the next. The last one is natural selection, through which successful strategies are passed to the next stage, and failed ones are eliminated gradually. In either two ways, successful strategy will survive and transfer their characteristics to their descendants, while unsuccessful strategies will be replaced. The feature of population, variation, selection, and reproduction exhibits the evolutionary characteristics of drug discovery process.

Along with the development of rational drug discovery, the complexity of knowledge has increased dramatically. Discovering a drug requires the integrated expertise of various areas, including screening, combinatorial chemistry, genomics, bioinformatics, drug delivery as well as numerous drug discovery methods such as monoclonal antibodies, oligonucleotide ligands, peptides and stem cell therapies (Rasmussen 2010).

R&D is obviously the crucial determinant for the companies' competitiveness in the current biopharmaceutical sector (McKelvey and Orsenigo 2001). There is an increasing number of companies relying on inter-organizational collaboration for their adaptation and learning in the changing environment. Biotechnology companies play an important role in exploring knowledge and collaborating with large pharmaceutical companies, which is believed to be a primary source of innovative knowledge for the pharmaceutical industry (Pyka and Saviotti 2001, Quéré 2004). The relationship between large pharmaceutical company and start-ups can be considered as an important means of adjustment of knowledge stock.

7.2.2 Modelling

Some research has suggested that the innovation process based on knowledge, such as drug discovery process, can be modeled in the context of search and optimization theory (Gambardella 1995). The first innovation model was introduced by Stigler (1961). Then the framework of modeling the innovation was set up by Dasgupta and Stiglitz (1980), and Nelson and Winter (1982). In our model, the drug discovery process is modeled as a knowledge evolution process, in which the drug is depicted as a collection of qualified knowledge and the discovery process is translated into an optimization knowledge process towards the qualification.

The model in Chapter 6 examined different paradigms of organizational learning, the ways in which organizations improve their knowledge set towards desired goals. In the previous experiments, it was shown that: firstly, the organizations learning through both exploitation and exploration performs better compared with the organizations learning through either exploitation or exploration; secondly, exploration maintains the diversity of the knowledge base, while exploitation contributes to the refinement of the knowledge base; thirdly, the output of organizational learning through different combinations of

exploitation and exploration at both intra-organizational level and inter-organizational level were observed.

Based on the above findings, the modeling of orphan drug discovery process is enlightened from the organizational learning model. The orphan drug discovery process is viewed as a learning process; the outcome of drug discovery is the embodiment of knowledge learned through exploration and exploitation. The existing knowledge is continually refined through exploitation while new creative knowledge is created through exploration.

7.2.2.1 How to model the drug discovery process?

The simulation model is built as an agent-based model (ABM). In the ABM, the organizations are represented by agents with a high degree of heterogeneity and bounded-rationality. The agents can be modeled as either isolated or connected with other agents. The agents have different behavioral rules they can show different learning configurations. The Genetic Algorithms (GAs) are applied in the model to simulate the optimization process.

The critical feature of the GAs is the ability to exploit accumulating knowledge about an initially poorly understood or unknown space to guide subsequent research (De Jong, 1988). The GAs are domain-independent search methods used to search the irregular and poorly understood space. The space to be searched in our model is the knowledge area about one of the rare diseases and related drug discovery technologies. The knowledge that the organization can obtain at the end of drug discovery process is affected by the initial knowledge base and the learning ability/strategy of the organization.

Moreover, the GAs reconstructs the evolution feature of drug discovery process in the model. The GAs has been widely used in a large number of fields to generate solutions to optimization and search problem. It captures the essential

features of variation, selection, and reproduction that are highly relevant in the biopharmaceutical innovation context.

The origin of GAs is a biological evolution. The evolution is a process not only existing in the domain of biology but also in the technical, social and economic systems. From the biological point of view, the evolution is any changes across successive generations in the inherited characteristics of the biological population. To address the evolutionary features of drug discovery, examining the key elements of evolution as originally developed by biology and demonstrating how drug discovery conform to these processes of GAs are necessary (Table 23).

Table 23 The Mapping of Biology, Genetic Algorithms and Drug Discovery

Biology	Genetic algorithms	Drug Discovery
Gene	Bits	Specific knowledge
Chromosome	Binary String	Knowledge
Population	Search Space	Collection of knowledge
Evaluation function	Fitness function	Safety and Efficacy
Selection	Selection	Exploitation
Reproduction	Crossover	Exploration (Innovation)
	Mutation	

7.2.2.2 Knowledge

Drug discovery is considered as a process of increasing the current knowledge base as well as optimizing the knowledge base through developing new knowledge. The knowledge here refers to the biotechnology or pharmaceutical knowledge, and manufacturing techniques.

The objective of the drug discovery is to find a promising drug, which has a high probability to pass the FDA clinical trial and obtain the marketing approval. FDA examines the drug through Preclinical Trial, Phase I Clinical Trial, Phase II

Clinical Trial and Phase III Clinical Trial based on the efficacy and safety data. The preclinical trial is usually done on animals to see whether the drug candidate works and whether it is safe enough to test on humans. Phase I Clinical Trial is conducted in a small group of healthy volunteers to evaluate the safety of the drug and examine the safe dosage range and side effects. Phase II Clinical Trial is conducted in a larger group of the patient population to measure whether it is effective for the condition it is intended to treat and further evaluate its safety. Phase III Clinical Trial is given to a large group of the population to confirm its efficacy, monitor the side effects, and compare it to existing drugs. After the successful conclusion of clinical trials, it will obtain the approval from FDA. According to the FDA standards, in our model, the quality of the drug candidate is evaluated by its degree of efficacy and safety. The fitness function is used to summarize the efficacy and safety of the drug and assess the qualification of a given drug.

The model simulates the whole drug innovation process from drug discovery to development. Therefore, all the drugs in the model are novel brand-name drugs. On one hand, orphan drugs have significantly less generic competition than other medications (Seoane-Vazquez, Rodriguez-Monguio et al. 2008); on the other hand, because of the complexity of most rare diseases and vulnerability of patients, the generic substitution of orphan drug is more challenging than non-orphan drug and should be undertaken carefully in rare disease patients (Di Paolo 2018).

At the beginning of each simulation run, every organization is set with a collection of N_k knowledge, which is implemented as binary bit strings with the same length. The more disciplines of knowledge an organization has, the broader its knowledge base is, and the bigger the number N_k is. Each piece of knowledge is composed of N_{bit} binary code (1 or 0). The strings are generated randomly to comprise the organizations' initial knowledge base. The amount of knowledge is constant during the whole process of simulation, which means once the new better knowledge is created, the worse knowledge is removed

from the collection. The removed knowledge is the less correct or less useful knowledge of the drug discovery.

7.2.2.3 Fitness function

Since the objective of drug discovery is specified, the status of knowledge at any time can be assessed by the fitness function. The quality of drug candidate represented in the organization's knowledge level can be determined by fitness function at each time step. The fitness of knowledge is calculated by the proportion of '1' in the binary strings (the summary of all the binary bits):

$$F = \frac{1}{N_k} \sum_{i=0}^{N_k} \left(\sum_{i=0}^{N_{bit}} bit_i \right) \quad (4)$$

The fitness lies between 0 and 100, and it can be interpreted as either a degree of correctness of the knowledge of a drug discovery project or the probability of the group finding the promising drug. For instance, the fitness value of knowledge A is 12, the fitness value of a drug discovery project is the average fitness value of the collection of knowledge the organization developed (Figure 33). At the end of drug discovery process, the fitness value is interpreted to the degree of safety and efficacy of the drug candidate; both are the requirements of FDA authorizing marketing approval. The average fitness value of the first fifty bits indicates the safety of the drug candidate; the average fitness value of last fifty bits indicates the efficacy. In the model, we assumed that if the organization finds a drug with $F \geq 80$, then the drug candidate is qualified to advance to the next R&D stage - drug development.

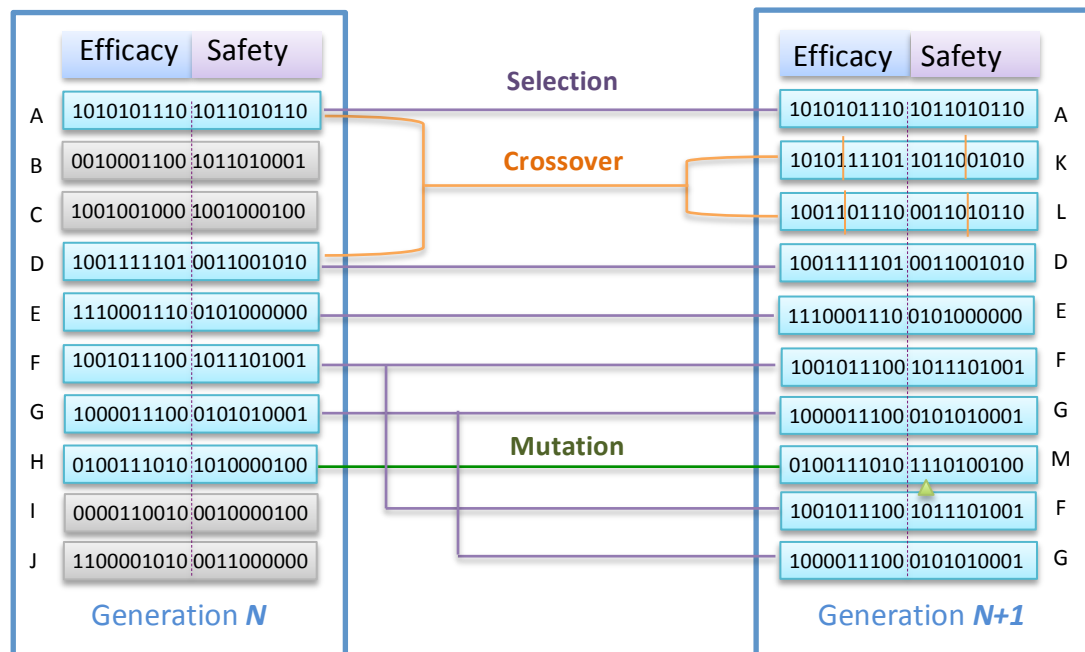
The knowledge level depends on the initial conditions and the parameters influencing learning. As the organization becomes more knowledgeable in the field of rare disease and the orphan drug they research on, there are more '1' in their knowledge set. An optimization is reached at which '1' account for more than 80% of the knowledge set. The outcome of drug discovery is calculated as

the average fitness of the knowledge, which is the same as the group performance is evaluated by the average of group members' performance.

7.2.2.4 Drug Discovery Process

The basic mechanism of drug discovery modeled by GAs is shown in Figure 33. Two simplifications are made in the figure to show the process more clearly: the first one is that each binary string has 20 binary codes instead of 100 in the model; the second one is that we show how the GAs work by exemplifying 10 binary strings in the population.

Figure 33 The Mechanism of Drug Discovery based on GAs



In generation N, there are 10 binary strings named from A to J, and as stated before, the number of binary strings in each generation remains constant during the process of GA. Their fitness value is calculated according to the fitness function, shown in Table 24. Since the crossover rate is 20% and the population size is 10, two binary strings (A and D) are selected by tournament selection method to reproduce offspring. Only 0.5%-5% of binary strings can be selected to mutate, and the mutation rate is dependent on the type of the company and

the strategy of R&D. In Figure 33, binary string H is selected to mutate, a bit of this string is randomly chosen (the 12nd binary bit) and modified from 0 to 1. In the Generation N+1, 3 new binary strings are created by crossover and mutation, 7 old binary strings with higher fitness value are selected from the past Generation N. The average fitness value of the collection is improved from 8 to 9.9.

Table 24 The Performance of GAs in Two Generations

Generation N					Generation N+1				
Item	Chromosome		Fitness	Action	Item	Chromosome		Fitness	
A	1010101110	1011010110	12	Selected / Crossover	A	1010101110	1011010110	12	
B	0010001100	1011010001	7	Eliminated	K	1010111101	1011001010	12	
C	1001001000	1001000100	6	Elimination	L	1001101110	0011010110	11	
D	1001100101	0011001010	10	Selected / Crossover	D	1001100101	0011001010	10	
E	1110001110	0101000000	8	Selected	E	1110001110	0101000000	8	
F	1001011100	1011101001	11	Selected	F	1001011100	1011101001	11	
G	1000011100	0101010001	8	Selected	G	1000011100	0101010001	8	
H	0100101010	1010000100	7	Selected / Mutation	M	0100101010	1010000100	8	
I	0000110010	0010000100	5	Eliminated	F	0000110010	0010000100	11	
J	1100001010	0011000000	6	Eliminated	G	1100001010	0011000000	8	
Average Fitness			8		Average Fitness			9.9	

7.2.2.5 Inter-organizational Learning

The previous sections showing companies innovating without network (intra-organizational learning), organizations discover the drug on the basis of its own knowledge base given at the beginning of the simulation run. In case of companies innovating through the network (inter-organization learning), organizations transfer the complementary knowledge among each other.

The procedure of inter-organization learning is as follows: 1) the organizations in the model have different collaboration strategies during the innovation process; biotechnology companies collaborate closely with research organizations in the drug discovery process and cooperate with big pharmaceutical companies in the drug development process while big

pharmaceutical companies seek to build alliance with biotech to expand their pipelines. In the model, based on the different collaboration strategies, the collaborative partners are selected randomly from the collection of objective collaborators, which could be a collection of research organizations, biotechnology companies, or pharmaceutical companies. 2) The organizations in the model have different degree of intent to collaborate with others. The biotechnology company is smaller and lack of experience, which makes it more flexible in building network than big pharma. In the model, biotechnology companies are set with higher intent to collaborate than pharmaceutical companies. 3) The number of collaborators determines the density of the collaboration network. The organization gets access to the complementary resources and knowledge from its collaborators. Therefore, with other factors being equal, the higher network density an organization has, and the higher the probability of driving the overall corporate success it will gain.

7.2.3 Experiment and Discussions

Experiments are conducted to simulate and observe the drug discovery process.

7.2.3.1 Different Periods of Drug Discovery

Experiment 4 is used to show the drug discovery process during different periods. The simulation setting of Experiment 4 is shown in Table 25. There are three models in this experiment. The first model is about the random screening period, organizations discover the drug within the organization based on limited knowledge and randomly screen the potential targets (INTRA-BT-V). The second model is about the rational discovery period. With the cutting-edge knowledge about genomics, molecular biology, and bioinformatics, organizations have more knowledge about the mechanism of the disease at the molecular level, so they changed from random screening to more rational drug design. Drug companies learn incrementally based on a broader knowledge base and through exploiting and exploring knowledge base (INTRA-BT-H'). The

rapid advances in science make the drug companies identify and unitize the externally generated knowledge. The third model is about the period of network collaboration. Drug companies usually take advantage of research conducted outside their organizational boundaries to get access to knowledge and other resources (INTER-BT-H-H').

Table 25 The Setting of Experiment 4

Period of drug discovery	Breadth of Knowledge Base	Organization	First period	Last period	Period (F \geq 80)
Random Screening	Narrow	INTRA-BT-V	20.200	76.227	–
Rational Design	Broad	INTRA-BT-H'	19.825	94.522	53
Network Collaboration	Broad	INTER-BT-H-H'	20.200	96.887	40

Figure 34 shows the differences of drug discovery in three periods. In the random screening phase, the knowledge is accumulated very quickly during the period from period 0 to 20, from period 20 to 40 the learning speed turns to slow down, from period 50 towards 90 the learning curve exhibits small waves. In the rational design phase, at the first 20 periods, organizations learn not as quickly as in the random screening period, but organizations keep learning at that speed and get a qualified drug candidate (F \geq 80) at period 53. In the network collaboration phase, organizations learn at the highest rate from the beginning till the period 40 when it discovers a qualified drug candidate.

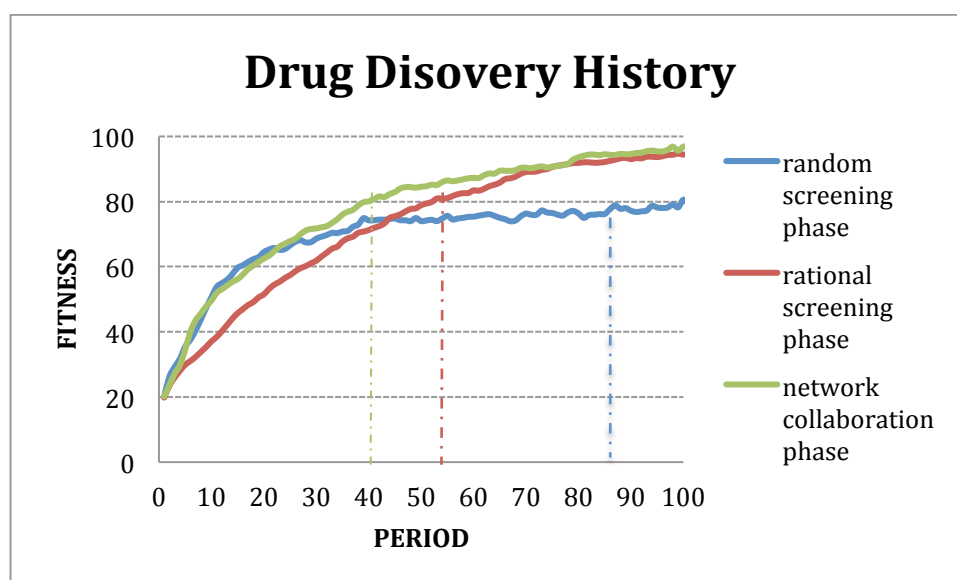


Figure 34 Different Ways of Drug Discovery in History

7.2.3.2 Discussions

We modeled the history of drug discovery from the 1970s. Drug discovery usually starts with identifying an appropriate drug target. Before the 1980s, drugs were discovered without knowledge about the disease (EXPERIMENT 1 INTRA-BT-V). A massive number of early discoveries in the pharmaceutical industry were through serendipity, where thousands of chemicals are applied to an assay that allows identification of compounds that produce the desired effect. Although companies can get many drug candidates quickly in the early stage, without the knowledge about the disease and the mechanisms of drug action companies get stuck in small fluctuations towards qualification as random screening these candidates in the late stage.

With the advance of biotechnology, from the 1980s, most targets currently selected for drug discovery are proteins that can be selected based on the understanding of human disease and the biotechnological process that lead to disease (EXPERIMENT 2' INTRA-BT-H'). There are two kinds of target: 'established targets' are those for which there is a good scientific understanding, based on several publications, and 'new targets' are those newly discovered

proteins or proteins whose function has now become clear through basic scientific research. Once a potential disease-causing target has been identified, a process of validation is carried out to examine the functions and effects of the target. From the simulation results, in the rational design period, the knowledge accumulation of finding a target at the beginning takes more time than finding drug candidates in random screening period, the knowledge about the disease linkage studies showing an association between the mutation in the biological target and certain disease states should be achieved. But it is more efficient in the following discovery stage of designing the molecules, or those are complementary in shape and charge to the target with which they interact and therefore bind to it. This period shows more rationality than random screening period.

From the 1990s, being centrally connected is essential for drug companies to achieve the valued innovation outcomes (Powell, White et al. 2005). Moreover, the extent to which companies learn about new knowledge and opportunities is a function of the degree of their participation in the collaboration (Levinthal and March 1993). For research organizations, strategic alliance is an excellent opportunity to commercialize their research discoveries; for biotechnology companies, it is a good strategy to obtain in-license knowledge created in research organizations and further develop and then transfer it to big companies that own the resources to commercialize the product; for pharmaceutical companies, it is a response to expected capacity because of patent expiration and gaps in pipeline. The alliance connecting research organizations, biotechnology companies, and pharmaceutical companies is to get access to the complementary specialized expertise. As the experiment shows, in this period, although the new knowledge obtained from outside increase the uncertainties of innovation compared with rational design period, the organization in the network learns at a higher speed.

7.2.3.2 Different Performance of Organizations

In the period of random screening, there are two main players: research organizations engaging in the basic research and pharmaceutical companies further discovering the drug based on trial-and-error learning.

Table 26 The Setting of Experiment 4

Organization	Breadth of Knowledge Base	Organizational Learning	First period	Period 80	Period (F>=80)
Pharmaceutical Company	Narrow	INTRA-BT-V	20.200	76.227	101
	Broad	INTRA-BT-V'	19.825	78.250	93

The setting of Experiment 4 is shown in Table 26, and the results of Experiment 4 are shown in Figure 35. During the random screening period, drug discovery is modeled as intra-organizational learning with a very high mutation rate and a narrow/broad knowledge base. The organizations with narrow knowledge base discover the drug candidate at the period of 101, and the organizations with extensive knowledge base exhibit better performance, finish drug discovery at the period of 93.

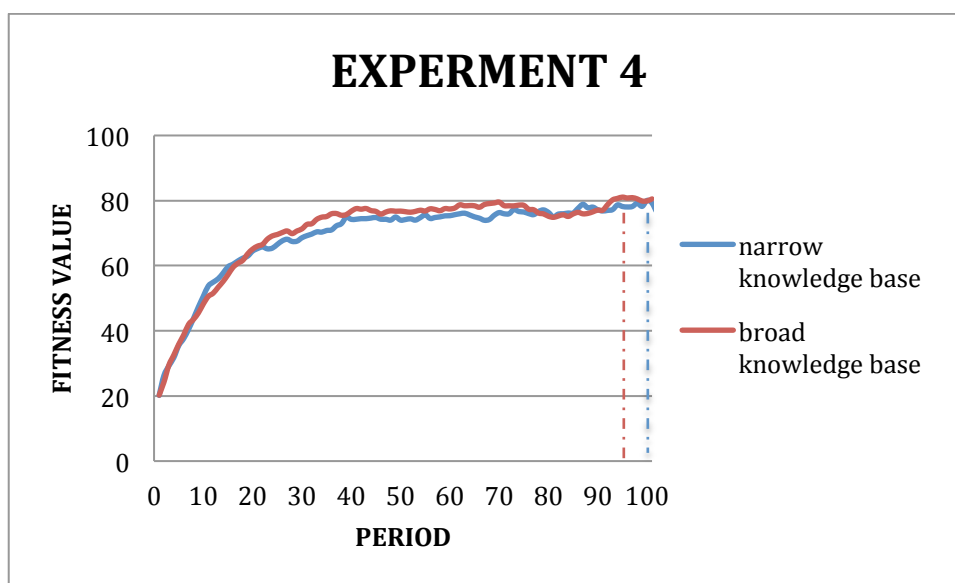


Figure 35 The Results of Experiment 4

Biotechnology companies emerged during the second period of drug discovery. They are featured with a specified knowledge base and the medium and high level of exploration. During the same period, pharmaceutical companies discover the drug with the lower level of exploration and broader knowledge base (Table 27).

Table 27 The Setting of Experiment 5

Organization	Breadth of Knowledge Base	Organizational Learning	First period	Last period	Period (F \geq 80)
Biotechnology Companies	Narrow	INTRA-BT-H	20.150	94.136	49
Pharmaceutical Companies	Broad	INTRA-BT-M'	19.825	65.205	–

As shown in Figure 36, the learning strategy of pharmaceutical companies is efficient during the random screening period, but in the new environment, the pharmaceutical company cannot achieve a drug candidate until period 100. However, biotechnology company exhibits a big advantage during the rational design period, and it discovers a potential drug candidate at period 49.

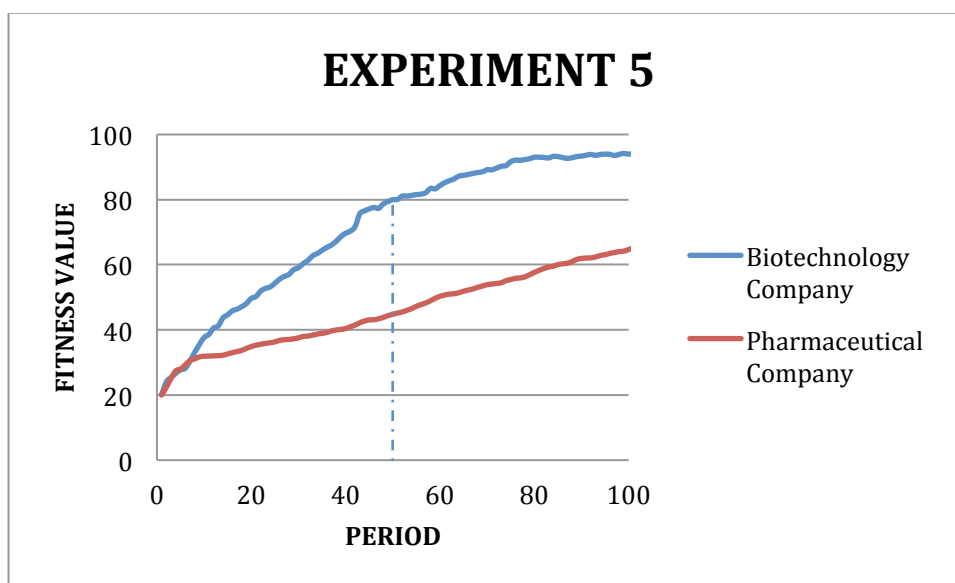


Figure 36 The Results of Experiment 5

In the network period, research organizations, biotechnology companies, and pharmaceutical companies conduct the drug discovery research with the connections with other organizations (Table 28).

Table 28 The Setting of Experiment 6

Organization	Breadth of Knowledge Base	Organizational Learning	First period	Last period	Period (F>=80)
Biotechnology Companies	Narrow	INTER-BT-H-H	20.000	96.636	33
Pharmaceutical Companies	Broad	INTER-BT-M-M'	20.025	91.978	69

Because of the collaboration with other organizations, pharmaceutical companies represent a better performance compared with intra-organizational drug discovery. Pharmaceutical companies discover the drug candidate at the period of 69 and biotechnology companies find the drug candidate at the period of 33 (Figure 37). The network facilitates the information flow among organizations, increases the speed of innovation, and minimizes risks by acquiring knowledge developed by others.

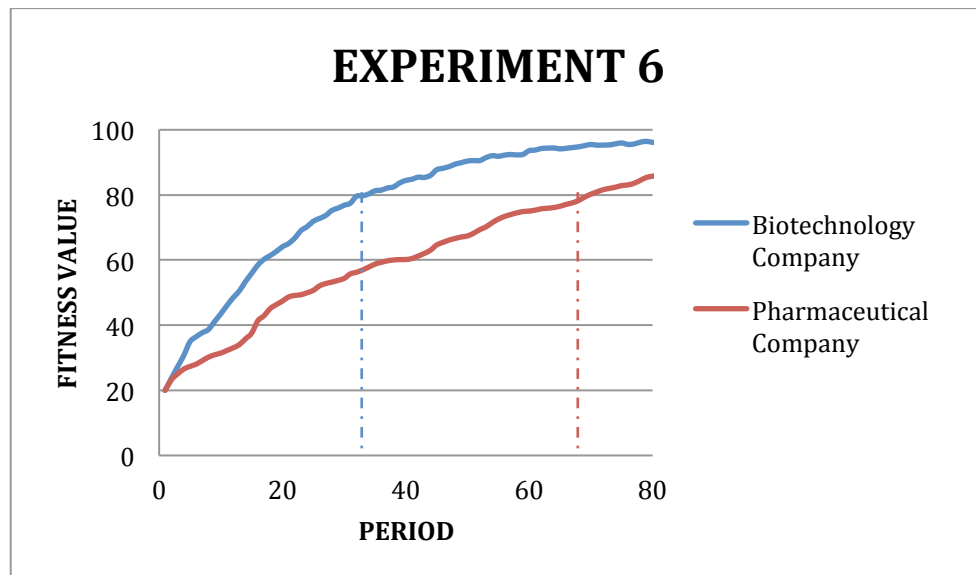


Figure 37 Different Performances of the Biotechnology Company and the Pharmaceutical Company in the Period of Network Collaboration

Discussions

The biopharmaceutical industry is a knowledge-based industry, and knowledge can be considered as the core dynamic capability of the firm and the principal driver of all other competence. Especially the biotechnology firms, they are founded and obtain investment on the prospects of transforming technological knowledge into potential economic benefits through the R&D and commercialization of an innovative product. Different performances among firms in the sector can be considered as the result of their knowledge base and capabilities of learning and developing knowledge. The factors influencing organizational learning are various, including culture, strategy, structure, environment, the organizational stage of development, and resource position (Fiol and Lyles 1985).

1. Research Organizations

Publicly funded research organizations have become more and more active at protecting intellectual property, spinning out new firms, licensing the technology to the private sector and developing their venture arms to support commercial development of their discoveries since 1970s. Universities and research institutions have contributed a lot to biopharmaceutical innovation. Research organizations are particularly good at creating novelty knowledge about disease processes. The learning strategy of them is more explorative, and their knowledge base is wider than other organizations.

The Bayh-Dole Act of 1980 stimulated universities to translate their academic research discoveries to commercial products. In subsequent years, many patents funded by public source have been licensed to the industry, resulting in the commercialization of hundreds of drug products. A large number of biotechnology firms are university spin-offs and established by scientists with their research outcomes. Many universities and institutions also provide university-backed venture funding and partnership with

business expertise from business school to encourage and facilitate the commercialization. Public research plays a significant role in providing fundamental insights into the sector as the foundation for further drug discovery, and with the drug discovery moved from random screening to rational discovery the role of public research has increased (Cockburn and Henderson 2001).

The academic research is especially important in the area where the market fails to drive the product R&D. Academic drug discovery is an ideal choice to tackle neglected diseases and orphan diseases; both of them have the limited market force to recoup the cost of development (Wyatt 2009). The drug discovery can be carried out using public funding at the beginning and then the project can be passed on to drug companies for further development. Moreover, academic drug discovery provides a test bed for the development of new techniques of drug discovery and the training of top scientists in the practice of drug R&D.

II. Pharmaceutical Companies

Knowledge and understanding of disease serve as a foundation for orphan drug R&D. From the results, we can find developing a few critical knowledge bases is of great strategic importance for drug companies. With a broader knowledge base, the company will be in a better position to learn and integrate related technologies. The more extensive a company's knowledge base is, the better performance the company will achieve in the random screening period (Experiment 4). This reflects the fact that big pharmaceutical companies dominated the sector before 1970 and they are still the influential player in the following period as they are rich in a broad range of science and technology and experience. The knowledge base includes not only rare diseases but also about other common diseases. In orphan drug R&D field, pharmaceutical companies have the advantages in repositioning approved drugs to orphan drugs. Since drug discovery is based on existing and prior knowledge, pharmaceutical companies can take

advantage of the rich knowledge base, large R&D team and good relationship with research organizations.

The advantage of a broad knowledge base not only benefits drug discovery but also helps a lot in drug development and marketing. Larger companies with diverse projects can share knowledge and experience about clinical trials among different projects within the company (Cockburn and Henderson 2001). Marketing a drug is also knowledge intensive. Business knowledge refers to the knowledge and skills of management, marketing, and relationship with other companies. Each drug is marketed with a comprehensive and costly campaign, so already established marketing infrastructure like marketing and distribution capability is very beneficial for the new drug launch (Rasmussen 2010).

The traditional innovation model of pharmaceutical companies lost its advantage in the rational design period compared with emerging biotechnology companies (Experiment 5). For biotechnology companies, due to their limited resources, one company only focuses on very few specific diseases, so that the company can become the leader in those areas. Most biotechnology companies are founded on only one drug R&D project in one particular area. However, pharmaceutical companies have the broader knowledge base, which results in the increased strategic flexibility and adaptability to environmental changes. Although orphan drug R&D was neglected by pharmaceutical companies before the 1980s, because of more expected returns of orphan drugs after 1983, pharmaceutical companies start to consider orphan drugs seriously to strengthen their R&D pipeline through the alliance, such as joint R&D project, merge and acquisitions, etc. Large pharmaceutical companies now play a critical role in the growth of orphan drugs. They account for over 50% of the orphan drug market, for instance, Abbott, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Pfizer, and Roche have more than two orphan products through acquisitions.

III. Biotechnology Companies

The biopharmaceutical sector is the innovation source of traditional pharmaceutical industry, while biotechnology companies have become the effective instruments of knowledge transfer to bridge the gap between academic research and big pharmaceutical companies (Drews 2000).

The most important resource of biotechnology companies is the highly expert scientists and specialized technology. The exploration characteristic of the biotechnology company is a dynamic capability to renew and adjust their research in response to rapid technology and market changes. It is also a significant competitive advantage of biotechnology companies (Experiment 5). On the other hand, biotechnology companies lack capital and experience, so they are struggling with taking the task of sales & marketing compared with large pharmaceutical companies. The impacts of marketing exclusivity protected by the ODA help biotechnology companies attract venture capital to invest in the long, risky and costly drug development process.

During the past several years, a rapidly increasing number of biotechnology companies have been focusing on orphan drug R&D. In the short term, biotechnology companies possess more motivations in taking advantage of the ODA incentives due to the limited capital and business scale. In the long run, given that pharmaceutical companies acquire biotechnology companies to fill their productivity gap, the promising biotechnology companies become attractive for big pharmaceutical companies. A majority of in-house projects of big pharmaceutical companies are driven by biotechnology companies acquired (Ashburn and Thor 2004).

Networking is vital for biotechnology companies (Experiment 6). Taking into the consideration of the fact that start-up drug companies face resource constraints, it is highly possible that they must depend on collaboration for access to knowledge and capital. For example, the biotechnology company

Biogen employed an exploration alliance with University of Zurich and an exploitation alliance with Schering-Plough to discover, develop and commercialize its product Intron A (Rothaermel and Deeds 2004). After biotechnology companies obtain a promising drug candidate, they should decide to develop it alone or collaborate with pharmaceutical companies that will commercialize the drug candidate if it approved. Big pharmaceutical companies have long-standing experiences and competencies to develop and commercialize new drug candidate through the regulatory process. Moreover, big pharmaceutical companies have adequate financial resources to afford this money- and time-consuming part of development process. The most alliances between the biotechnology company and pharmaceutical company are built when the new drug candidate is going to enter the phase of clinical trials (Pisano and Mang 1992).

7.3 Drug Development

The key steps of biopharmaceutical sector along the value chain are drug discovery, drug development and sales & marketing (Figure 38). These steps also reflect the evolution of knowledge value chain.

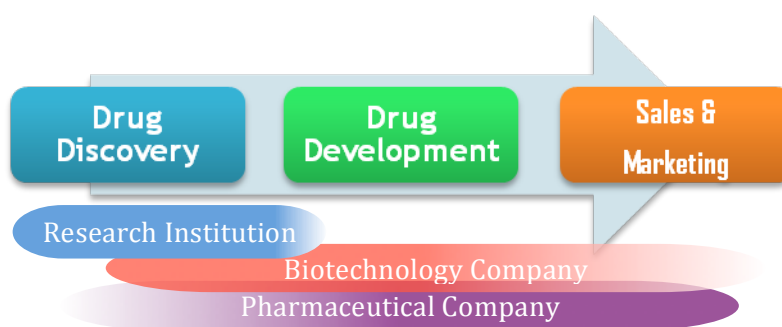


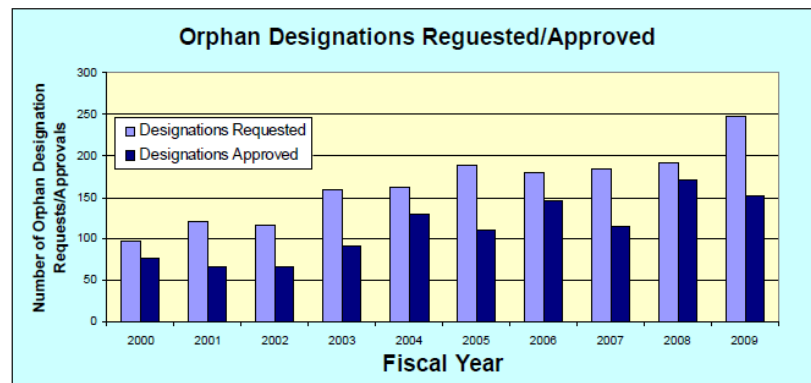
Figure 38 Key Steps of Value Chain in Biopharmaceutical Sector

But in the case of the orphan drug, applying orphan drug designation from FDA is a critical step, because only the drug with the orphan designation is entitled to have the 7-year market protection, grant aid, and other supports.

7.3.1 orphan drug designation

During the period from drug discovery to development, a sponsor (drug company) with a promising candidate submits the application for orphan drug designation to FDA. In our model, we assume that drug companies apply the designation before drug development. FDA gives more than one sponsor with orphan drug designations for the drug treating the same rare disease or condition. Due to the small market of orphan drugs, we assume that if sponsors fail to obtain orphan designation for their candidate, they will not continue to develop this candidate and go back to start another drug R&D project.

During the period from 2000 to 2009, nearly 70% of orphan drug designation requests are granted orphan drug status (Figure 39). The average time for orphan drug designation application is 1.5-2 years, but the drug R&D can be conducted at the same time. The time of designation application is 0.25 in the model.



(Source: FDA)

Figure 39 The Designations and Approved Designations of Orphan products

No matter what the result of orphan designation application is, the cost of the application is so small compared to the drug discovery and development cost that we can assume it equals to zero in our model.

The cost of drug designation:

$$CDES = 0 \quad (5)$$

7.3.2 Drug Development

In the model, once firm obtains the orphan designation of Candidate **Cad** from FDA, the drug company starts to develop the drug to obtain marketing approval. The drug development process is very risky in that the majority of the drug candidates that undergo tests are abandoned without obtaining marketing approval at the end.

Orphan drugs need to complete 4-step development, **STEP₁** is Preclinical Trial, **STEP₂** is Phase I Clinical Trial, **STEP₃** is Phase II Clinical Trial, and **STEP₄** is Phase III Clinical Trial. Each step costs a certain amount of expenditure and time. At the end of each step, the drugs with lower efficacy and safety than the requirements are not qualified to be tested on the next trial.

According to FDA data, from 1983 to 2009, there were 2116 drugs treating rare disease obtaining orphan designations, of which 16.7% (353) passed FDA approval. That means 16.7% of the designated orphan drug can obtain market approval and go to drug commercialization phase. After the ODA amendment in 1988, the time from orphan drug designation to FDA approval was 4.0 ± 3.3 years (Seoane-Vazquez, Rodriguez-Monguio et al. 2008). Accordingly, the average success rate and duration of each step are set in Table 29.

Table 29 The Parameter of Orphan Drug Development in Each Stage

The Step of Orphan Drug Development	Average Duration (year)	Efficacy Requirement	Safety Requirement
Drug Designation	0.25	-	-
Preclinical Test	0.25	-	38
Phase I Testing	0.5	38	39
Phase II Testing	1	38	40
Phase III Testing	2	40	40

There are many factors influencing the cost of drug development process. The first one is the Efficacy E and Safety S of the candidate; both determine the results of FDA orphan drug approval. Each step has an attrition rate, and if the drug company has enough capital and the Efficacy E and Safety S of the drug candidate is higher than the requirement, this candidate can get the market approval. The second one is the Prevalence PVL of Indication I_n , $PVL_n \sim U(1, 200000)^2$. Obviously, candidates differ in the cost and time of their development process: lower prevalence implies lower time and cost with high possibility.

The cost of $STEP_y$

$$CDEV_{ny} = (0.67 + 0.1 \times Lg(PVL_n^*)) \times \tau_y \times BUD_{dev} \quad (6)$$

The time of $STEP_y$

$$TDEV_{ny} = \tau_y \times (t_{dev} + 0.5 \times Lg(PVL_n^*)) \quad (7)$$

Standardized Prevalence

$$PVL_n^* = PVL_n / 200000 \quad (8)$$

7.3.3 Experiment

The basic setting of the experiment is

- There are 15 biotechnology companies, 5 big pharmaceutical companies and 10 research organizations at the beginning of the simulation. Every ten time-step, one biotechnology company and one research organization enter the orphan drug innovation system; every twenty time-step, one big pharmaceutical company enters the orphan drug innovation system.
- To better observe the model at this stage, each organization conducts one orphan drug R&D project at the same time, if the drug candidate is not qualified at the end of each state or the organization run out of

² The parameterization of PVL is shown in Appendix 3.

money during R&D, which leads to the R&D project fails and the organization quits the simulation.

The experiment shows that there are 45 orphan drug R&D projects in total; only 16 qualified drug candidates are discovered (Figure 40). The average duration of drug discovery is about 9 years.

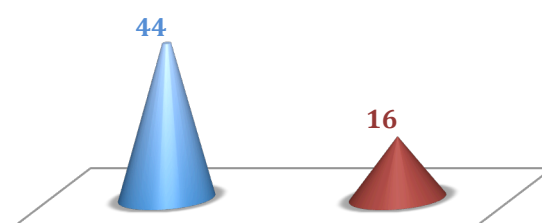
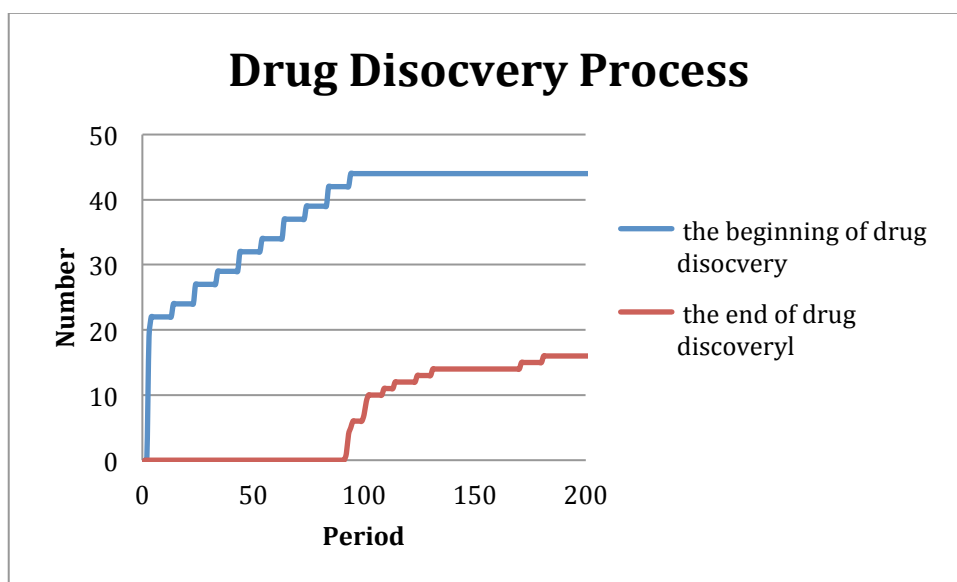


Figure 40 The Drug Discovery Process

Figure 41 shows the number of drug candidates in each drug development process. There are 16 drug candidates examined through pre-clinical test, and 15 of them pass the test. Finally, 5 drug candidates get the FDA approval, so the success rate of orphan drug development is 32%.

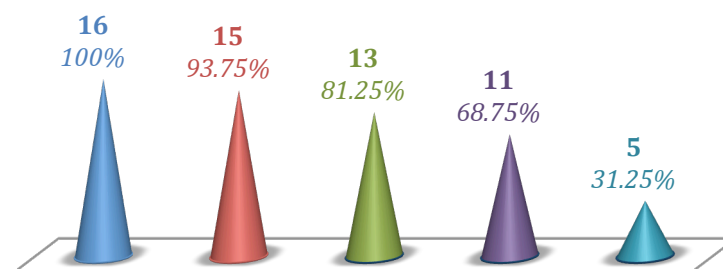
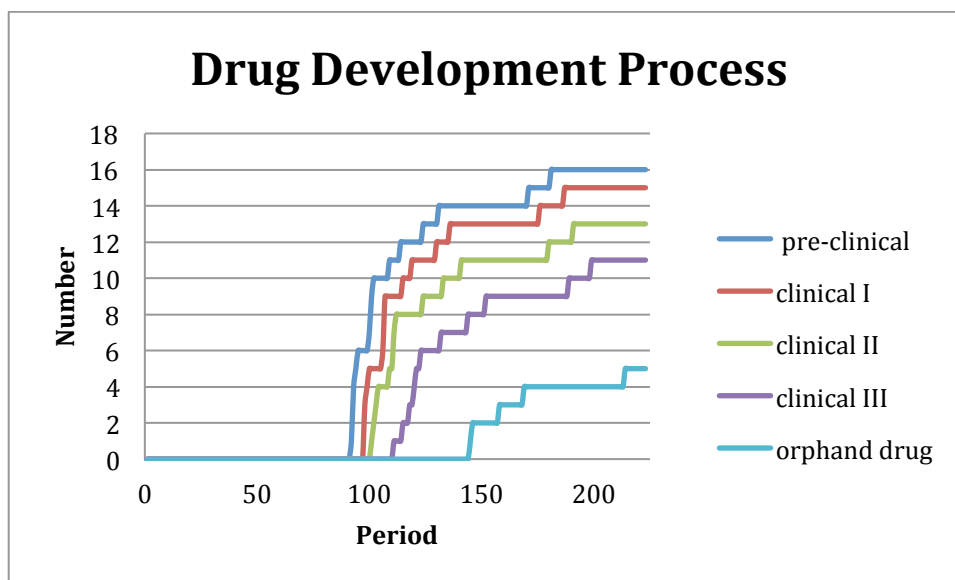


Figure 41 The Drug Development Process

7.4 Drug Commercialization

Before the ODA, drug companies rely on the patent to protect the technology and market of their products. Drug companies typically apply for a patent, which precludes other firms from acquiring a patent on the same drug and selling it. The biotechnology companies rely heavily on sufficient patent protection to recover the costs of R&D from sales and to attract investors to invest in. A number of orphan drugs are not patentable, and even some drugs have already been patented before, so market exclusivity is of significant value for orphan drug. It makes the small orphan drug market with big potential. Hence, market exclusivity is the most important factor influencing drug

commercialization. Moreover, there are three main issues concerning the orphan drug commercialization.

7.4.1 Cost

The cost of discovery and development of a new drug was estimated to exceed \$1.3 billion in 2006 (DiMasi and Grabowski 2007). The cost structure of the pharmaceutical industry is much different from other sectors. Firstly, drug R&D involves a significant amount of sunk costs. Drug companies have a very high upfront cost of R&D and commercialization cost, but sunk costs also stem from the high rate of failure. Second, the marginal cost (manufacture) of drugs is relatively low. Third, a high return should be achieved to offset the high cost of R&D.

7.4.2 Market

Because of the high cost of discovery and development and the small probability of success for each drug candidate, drug companies should work extensively on the marketing to ensure their share in the competitive market. Whether the approved drug delivers considerable return and profits to the company depends on their ability to set a reasonable price and sufficient sales volume over the period of market protection. The condition is slightly different in the orphan drug marketing, as the active networked relationships among patients, advocacy groups and an experienced body of medical expertise make market penetration faster than non-orphan drugs. Moreover, there is less need for advertising and large sales efforts to prompt the drugs. As discussed before, the cost of orphan drug marketing is much lower than the non-orphan drug.

7.4.3 Pricing

The price paid for a medicine comprises some components. Along the supply chain from manufacturer to patient, various components are cumulatively

added into the manufacturer's selling price (MSP), such as freight costs, taxes, markup, and procurement fee. The sum of these fees is not low, accounting for 30%-45% of the dispensed medicine price on average, and it can be much higher. In our model, drug pricing refers to the price set by the manufacturer. The price of the orphan drug is set to recoup the research, development and marketing cost and to acquire a certain profit. Moreover, the pricing of the orphan drug should account for the efficacy and safety of the product, the value of the drug delivering to patients, market conditions and regulatory and reimbursement factors. Moreover, the price of the orphan drug is influenced by the following factors:

1. Fundamental new medicine with major clinical significance.
2. Important new medicine offering a substantial advantage for the majority of patients.
3. Basic new medicine offering the advantage for the minority of patients.
4. New medicine offering an only marginal advantage over previously available medicines.
5. New medicine offering little or no advantage over previously available medicines.

7.4.3.1 Orphan drug pricing

Drugs with higher pricing and adoption rate in life-threatening conditions can overcome small patient size, and the orphan drug is one of them. In our model, we consider three main factors influencing the price of the orphan drug.

- **COST** Different drug discovery and development strategies will result in different products with different cost. We only consider the R&D costs in our model.
- **VALUE** The evidence of efficacy and safety are significant in evaluating the value and setting the price of medicine (Gregson, Sparrowhawk et al.

2005). Clinical trial data, especially the Phase III trial is the primary evidence of demonstrating the value of a new medicine. Drug companies charge a price premium for higher efficacy and safety and obtain higher financial returns. In our model, the value of the drug is evaluated in terms of effectiveness and safety based on the pharmacological and clinical performance.

MARKET POSITION The market position of the new product is one of the leading factors for pricing. The market of the drug is determined in the early stage of drug R&D. The start of drug discovery is choosing the indication, and it is evident that a different indication generally refers to different groups of customers, competing products, dosages, and durations.

Developing innovative products is the primary objective of many firms. The medicine with the preferred market position is the primary incentive for the objective. The market position ranges from strong market power (newly patented drug) to perfect competition (generic drugs). After the launch, 7-year market protection allows drug companies to charge a monopoly price over the marginal cost and make an enormous profit to recover the cost of drug development and give motivation for companies to develop the orphan drug.

In general, based on the market situation, there are three main pricing strategies usually used by pharmaceutical companies in the free-pricing market. If the drug is the first treatment on the market, the first strategy is to price the product at a comparatively high level when the product is launched initially and then gradually reduce the price during the lifecycle of the product. If there are already some drugs treating the same disease on the market, the second strategy is to set the price of the new product the same as the products already on the market, this strategy. The last strategy is to price the new product lower than existing products in the market.

Orphan drugs have fundamentally distinct commercial challenges compared with traditional products. Low prevalence represents the most challenging drug pricing situations. Orphan drug pricing must consider two factors: recoup high-risk research investment and ensure patient access. Some drug companies take advantage of the status assigned to orphan drugs by the ODA to increase their prices, at levels far beyond the costs of R&D and manufacturing. Hence, some of the orphan drugs have become the biggest moneymaker for biotechnology companies, such as Genzyme and Genetech.

7.4.4 Revenue Flow

The economic return generated from drugs is highly skewed, since the sales of a small number of blockbusters dominate the pharmaceutical market (Rasmussen 2010). In the model, we assume that the cost of drug manufacture, distribution, and marketing is zero. Once the candidate gets the market approval, it can immediately be sold on the market. The pricing of the orphan drug shares the same economic logic as pricing of the common drug.

In our model, we do not simulate the pricing decision explicitly; instead, we assume that drug companies will set a price based on some factors. According to that, we use ‘Merit’ U to evaluate these factors influencing the commercialization of the orphan drug.

$$U_{mn} = (E_{mn} + S_{mn})^a (1/\gamma)^b C_{mn}^c M_{mn}^d \quad (9)$$

E_{mn} and S_{mn} is the indicator of drug’s *Efficacy* and *Safety*. γ is the expected rate of return that drug company expects to get from its product. Given other factors are same, the bigger the desired return is, the higher drug price will be set and the lower the demand will be in the market. C_{mn} is the R&D investment of company m for drug n , M_{mn} is the market situation company face. The value of exponents a , b and c are dependent on the Indication I and follow the uniform distribution.

In the environment of competition, the original innovator will compete with other product. Therefore, the price and market share will be lower than before. The market share MS_{mn} is

$$MS_{mn} = U_{mn} / \sum U_I \quad (10)$$

The Price P_n is expressed by the drug's price P^* , which is set according to the total R&D cost and condition of the perfectly competitive market. But the biopharmaceutical market is not the perfectly competitive market. The U_{mn} is the price indicator of company m on drug n , so the price P_{mn} is set as

$$P_{mn} = U_{mn}^f \times P^* \quad (11)$$

7.5 Orphan Drug Act

The ODA has offered several incentives to motivate the orphan drug R&D, such as market exclusivity, tax credit, approval guidance. The 'Governance' agent is set to simulate the incentives provided by the ODA.

7.5.1 The Influence of the ODA

Market Exclusivity

According to this incentive, drug companies can charge a monopoly price on the drug in the US market during the 7-year period after obtaining market approval. The price is regulated by competition after the expiration of 7-year market exclusivity.

Given that the number of patients is same, the price drug company charged on drug n changes according to the monopoly market position stemming from the market exclusivity and the competition among companies after the market protection. Market exclusivity protects the drug from competition in the same

indication during a specific duration. Drug companies can charge a monopoly price in the first seven years

$$P^{n7} = \mu \times U_{mn}^f \times P^* \quad (12)$$

μ is the monopoly rate, drawn from a uniform distribution ranging between 1 to 3.

In the first 7 years, orphan drug faces no competition because of market exclusivity, and it dominates the whole market. But with the increase of drug price, the demand for orphan drug will decrease. The market share of this drug is

$$MS_{mn}^{n7} = 0.95^\mu \quad (13)$$

Grants

FDA has invested over \$246 million in orphan product grants, which have contributed to approximately 28% of designations and 15% of approved orphan drug (Milne and Tait 2009). The funding of research institutions accounts for most of the grants for orphan drug discovery. Every period of simulation, there will be five new grants to support research institutions finding a promising candidate. The value of this grant is set randomly as the initial research budget.

$$G_{dis} \sim U(1000, 2000)$$

Grants also support drug companies to do the clinical studies for no more than three years for Phase I trial and no more than four years for Phase II and III trials. About only the 15% of drugs under development can be supported by orphan product grant. Φ is the grant index drawn from the uniform distribution from 10% to 40%.

$$\Phi \sim U(10\%, 40\%)$$

Accordingly, the cost of **STEPy** ($y=2,3,4$) is

$$CDEV_y^\Phi = \Phi \times CDEV_{ny} \quad (14)$$

Tax credit

The tax credit is normally half the costs of clinical testing on all orphan drugs, including both successful and unsuccessful products under drug development. So, the cost of drug development after tax credit is 50% of qualified clinical testing expenses paid. The tax credit does not apply to the drug development already funded by a grant and the drug companies whose activities are engaging in drug discovery and development without ‘carrying out any trade or business.’ At the beginning of the simulation, we assume that all the large- and medium-sized pharmaceutical firms and large-sized biotechnology firms have the approved drug in the market, so they can benefit from this provision. Once small-sized pharmaceutical companies and medium- and small-sized biotechnology companies have one approved orphan drug, they can get the 50% tax credit for the clinical trial. So, the clinical trials of medicines satisfying the requirements can be supported by tax credit. θ is the tax credit index.

$$\theta = 50\%$$

The cost of *STEP_y* ($y=2,3,4$) drug development is

$$CDEV_y^\theta = \theta \times CDEV_y \quad (15)$$

Fee waiver

FDA can waive fees under five different circumstances, one of which is the drug gets the orphan designation. In our simulation, all the drugs in development phase are awarded orphan designations and compared with the significant amount of R&D costs, the fee waiver is ignored in the model.

Approval Assistance

The assistance from FDA, increase the success rate of drug approval. 80% of the drug development project can benefit from this incentive, with 10% decrease in the original thresholds for efficacy.

$$\delta_1 = 0.45 \quad \delta_2 = 0.55 \quad \delta_3 = 0.65 \quad \delta_4 = 0.75$$

In all, the parameters are called the Standard Set, which not only indicates some fundamental characteristics of the orphan drug sector but also presents the orphan drug innovation system in a highly qualitative way. These settings of the parameters and their values of the model are based on the reality and several strongly simplifying assumptions.

Market Entry

The entry is defined as the date of the firm's founding. In order to start a biotechnology company, companies should consider four factors—expertise in scientific research, management skills in business, sufficient cash flows and at least a promising product. The main barrier to market entry is the high amount of funding to finance their massive R&D budget. The early-stage biotechnology companies can get access to research funding from numerous programs. Venture capital firms play a significant role in financing start-up biotech companies, but half of them are supported by venture capital (Burns, Housman et al. 2009). However, it needs to undertake strategic planning for its further development.

The majority of funding is used for R&D purposes. To raise funds, many companies seek venture capital, partner with big pharma, or other companies, or secure help from angel investors and government or small business grants (Tsai and Erickson 2006). Biotechnology companies need to achieve R&D milestones on time and on budget as well as meet the needs of investors.

A small number of biotechnology companies in the sector are extremely profitable, which drives the entry of a large number of competing companies and inflow of capital. And while the potential for generating free cash flow on a product is promising, biotechnology companies are hard to keep their share of the profit or the ownership of the company. Because of high technical risks, long R&D horizons, and big capital demand lead to biotechnology companies that compromise their ownership in exchange for funding from venture capital and corporate partners.

In conclusion, there are three factors influencing the market entry of biotechnology and pharmaceutical companies: technology, capital, and environment. Technology (*Tech*) is the prerequisite, companies have to get a great idea for a biotech product to start a biotechnology companies; capital is the lifeblood to the industry, and it is the foremost focus of biotechnology companies; the least but most important is the environment, in which good investment climate (*Invest*), profitability of current companies (*Profit_{3-year}*) and public support (*Public*) will drive more companies to enter into the market.

$$ER_{res} = f(Tech, Public) = \frac{(Tech + Public)}{100} \quad (16)$$

$$\begin{aligned} ER_{bio} &= f(Tech, Profit_{3-year}, Invest, Public) \\ &= \frac{(Tech + Profit_{3-year} + Invest + Public)}{100} \end{aligned} \quad (17)$$

$$\begin{aligned} ER_{big} &= f(Tech, Profit_{sec}, Public) \\ &= \frac{(Tech/2 + Profit_{3-year} + Public)}{100} \end{aligned} \quad (18)$$

$$Tech \in (1, 2, 3, 4, 5)$$

$$Public \in (1, 2, 3, 4, 5)$$

$$Public \in (1, 2, 3, 4, 5)$$

Market Exit

The exit is defined as the unsuccessful dissolution of the firm (bankruptcy), or the dissolution of the firm (acquisition and merge by another company). The large incumbent firms, like big pharmaceutical companies, are more conservative and at the same time eager to keep their technology advance. Therefore, they acquire smaller new entrants to fuel their growth through combining the innovative technology of new entrants with their established marketing and distribution channels. During the simulation, we can see some new biotechnology companies enter the industry and some old biotechnology

companies exit because they lack money to continue the project or the big pharmaceutical companies acquire them.

The entry and exit rate are important for public policy reasons: firstly, the pressure of new entry and the risk of exit stimulate incumbent firms to compete and the competition will drive the cost down and the quality up, which will benefit the customers; secondly, the entry and exit of companies increase the diversity of industry. Moreover, it prompts technological learning and innovation at the firm level, but at the same time, it also advances positive evolution at the industry level.

7.5.2 The Influence of network

This experiment is conducted based on the conceptual model of drug discovery and development model presented in chapter 3 and 4.





7.5.2.1 The network of the system

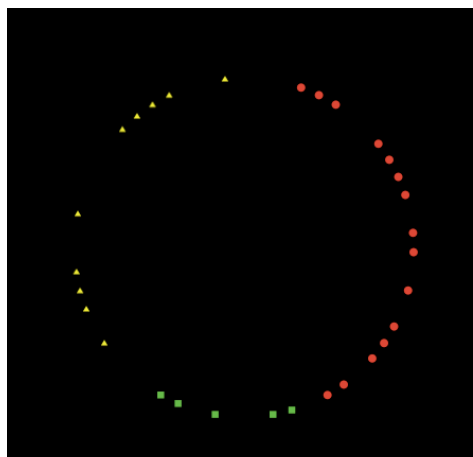
The organization in the system collaborates to get access to complementary resources. When companies run out of money, they will seek financial support from other companies with abundant capital in the system; when research organizations want to commercialize their research outcomes, they will collaborate with drug companies; when companies need the complementary knowledge from other organizations, they will find a partner in the system to access the knowledge; and the research organization can build up a spin-off company to continue the drug R&D project. In the model, collaborative partners were chosen randomly from a collection of the qualified organizations.

During the simulation process, there are new biotechnology and pharmaceutical companies entering the industry. Figure 42 shows the evolution of the collaboration network in the orphan drug innovation system. In panel b. of Figure 42, the network shows the collaboration among the organizations after

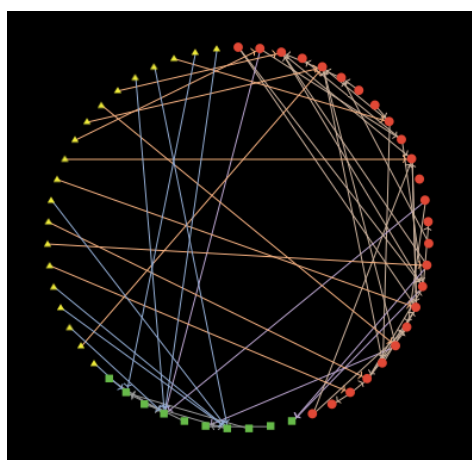
200 time steps. The orange line indicates the collaboration between a research organization and a biotechnology company; the pink line indicates the collaboration between a pharmaceutical company and a biotechnology company; the blue line indicates the collaboration between a pharmaceutical company and a research organization; and the brown line indicates the collaboration between biotechnology companies. Figure 42c, the network layout of figure 42b, shows the distribution of the organizations in the system.

Figure 42b and 42c show the collaboration network in the open innovation system; b' and c' show the collaboration network when the inter-organizational learning is not free. From comparing c and c', we can see that the network concentration of c' is lower than c, especially in the number of collaborations between biotechnology companies.

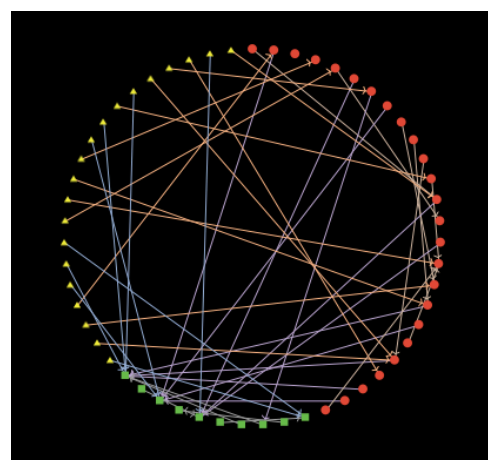
 Research Organization
 Biotechnology Company
 Pharmaceutical Company
 Collaboration between two organizations



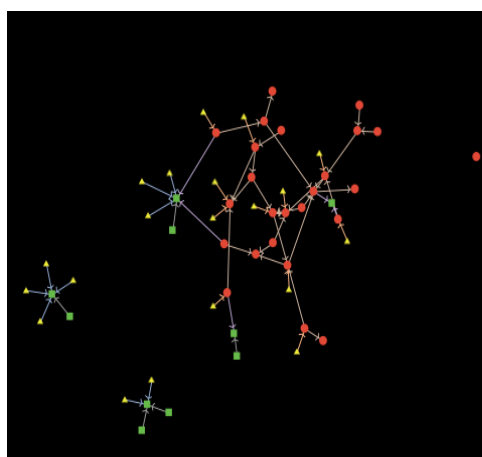
a.



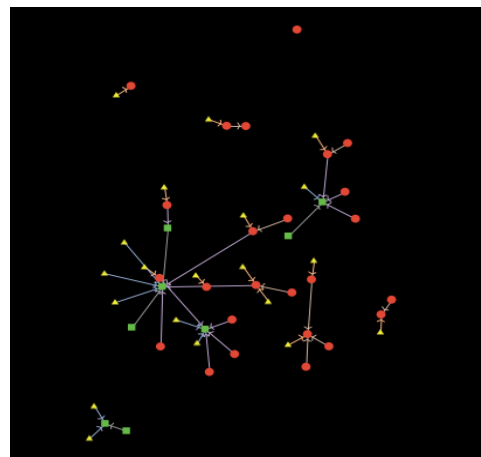
b.



b.′



c.



c.′

Figure 42 The Network of Biopharmaceutical Industry

7.5.2.2 The Influence of the ODA

Figure 43 shows the orphan drug discovery and development under the protection of the ODA. Compared with Figure 41 that shows the orphan drug discovery and development without the protection of the ODA, there are more drug candidates at each stage of R&D and more orphan drugs available on the market.

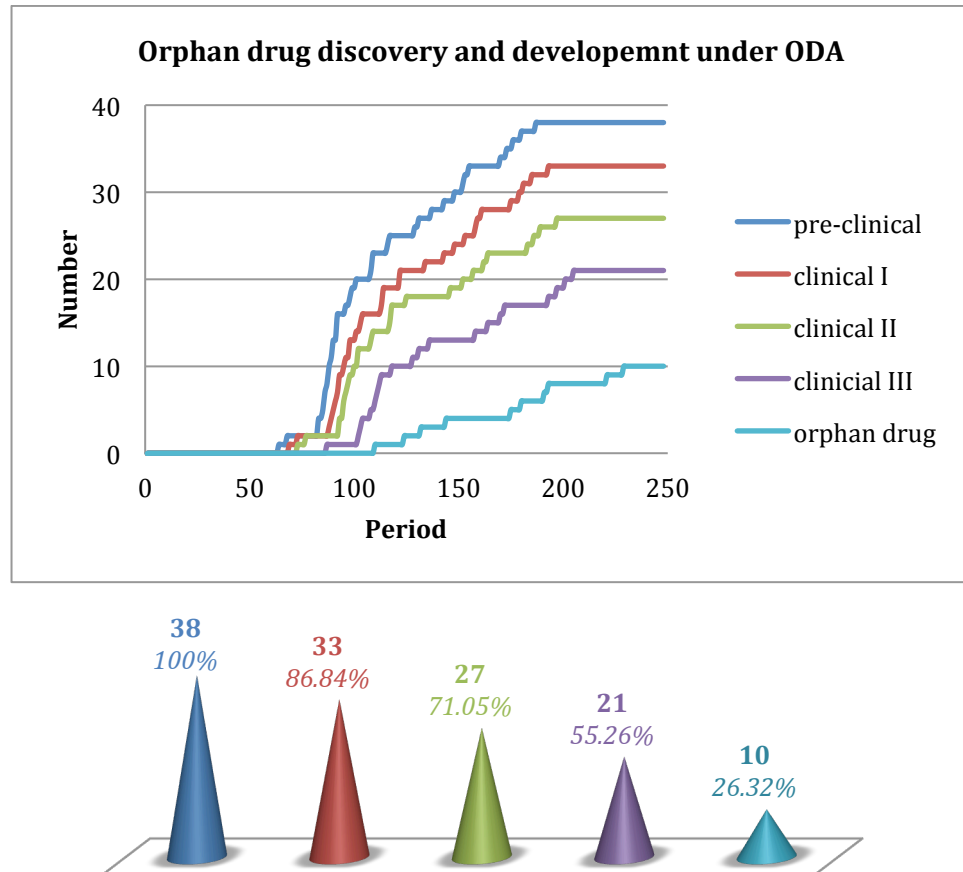


Figure 43 The Influence of the ODA on Drug Discovery and Development

7.6 Summary

The model in this chapter is the first model simulating the evolution and dynamics of the orphan drug innovation. It has been built to attain a holistic

understanding about sectoral innovation and the influence of public interventions.

Our results have demonstrated that the ODA is an important factor in orphan drug innovation and shortening the 7-year market exclusivity will change the current prosperity of orphan drug innovation. Any drug company intending to enter the sector is reluctant to see a decrease in the period of market exclusivity because market exclusivity is the only incentive that is exclusively beneficial to these drug companies. The inappropriate change in market exclusivity would decrease new entrants and the exit of incumbents.

The adoption of multi-tier rights should be applied to the orphan drug legislation in order to encourage more effective innovation. The solution purposed for the US ODA is to make it multi-tiered, which operates in conjunction with the other incentives offered under the current ODA. Therefore, the multi-tiered ODA is a supplementary provision to the current ODA.

The multi-tiered nature of the ODA is a superior incentive to the market exclusivity in both theoretical and practical terms. Firstly, it addresses the criticism around the ODA, which include 'blockbuster' drugs that have been immensely profitable; the 'salami slicing' through which drug companies can obtain multiple orphan drug designations; and the 'over-broad scope' of the market exclusivity. Secondly, the multi-tiered ODA still keeps the majority of rights for the industry while it offers substantial benefits to the public. This would create a more equal and competitive environment for the orphan drug innovation and would encourage subsequent innovations that will improve upon the original orphan drugs. Through the elimination of the 'winner-takes-all' system of the market exclusivity, which means only the first drug approved with orphan status will be awarded market exclusivity; more companies would be willing to invest in orphan drug discovery and development. This change would be helpful for the sustainable development of the sector and for the patients to get more effective and less expansive drugs quickly.

Chapter 8 Conclusion

8.1 Introduction

In knowledge-intensive sectors such as the pharmaceutical industry, companies can no longer achieve successful innovation by themselves, and cooperate with other organizations in the network. Moreover, the performance of system exhibits emergent characteristics as the collection of the individuals' behavior brings about phenomena at the aggregate level that goes beyond the sum of individuals. Actors in the system create and shape the network through their decisions and activities. Simultaneously, the structure of the whole network and the position of actors in the network influence the actors' behaviors through connections and feedbacks. Actors engage in decision-making and respond to the environment and network they are embedded in. Such a system with interactive relationships can be considered as a complex adaptive system that evolves dynamically over time.

Pharmaceutical research had evolved dramatically in the past decades. Developments in science and technology contributed substantially to the increase in life expectancy and quality. Nevertheless, bringing a new drug to the market today still involves not only a variety of knowledge including molecular biology and chemistry genetics, but also a large number of environment forces, such as economics, market, politics, and laws.

The pharmaceutical industry is a knowledge-intensive sector, in which knowledge is the core component. In order to understand the system thoroughly, we need to start from 'knowledge', which plays an essential role in the innovation process, but what happens to the knowledge in the system remains mostly unclear. One of the objectives of this research was to build a model to investigate the knowledge dynamics in the SI. A particular focus was to apply this model to address orphan drug innovation system with the second

objective of exploring the systemic dynamics in this unique sector. We hereto proposed a framework, in which two types of knowledge (incremental knowledge and radical knowledge), learning patterns (exploration and exploitation), and organizational learning (intra-organizational learning and inter-organizational learning) are distinguished. Based on that, we investigated and explored the dynamics of organizational learning and how different learning strategies influence the knowledge output of the organization.

Through agent-based modeling, this thesis sought to improve our knowledge about the innovation of knowledge-intensive sector as a complex adaptive system. It explored the various forces bearing on the innovation of orphan drug in the US, especially the influence of the ODA. The primary aim of this research was to investigate and explore the dynamics of orphan drug sectoral system of innovation (SSI) in the US. To reach this aim, the theoretical foundations adopted in this research moved beyond the linear, non-linear, and network models of innovation that had dominated the system of innovation literature. The theoretical framework comprises: 1) the system of innovation theory, which is regarded as the most comprehensive perspective of innovation process; 2) the knowledge-based view of firm, which complements the system of innovation theory on the micro-level analysis; 3) the complex adaptive system of innovation, which helps to bridge and complement the former two theories in terms of dynamics and emergent features. The combination of these three theories comprises the theoretical framework of the orphan drug innovation model.

Chapter 1 represented a brief background about the research and the objective of this research. Chapter 2 provided the overall literature review on the system of innovation with knowledge-based innovation and models related to the creation of knowledge-based innovation. Chapter 3 introduced the pharmaceutical innovation process in different periods. The ODA, as the most critical factor influencing orphan drug innovation in US was presented in Chapter 4. The research method of social simulation, the simulation model of

Agent-based Model and the modeling toolkit, NetLogo, were introduced in Chapter 5. Based on the conceptual framework proposed in Chapter 2, reflecting on the preliminary findings in Chapter 3 and 4, and according to the research design in Chapter 5. Chapter 6 described how to build the orphan drug innovation model and how the model functions. In the last chapter, Chapter 7 laid out the results and arguments gained through the simulation.

This chapter begins by re-examining the research aims set up at the beginning of the thesis and highlights the main results of research. This is followed by a summary of the key findings and their implications. The contribution to knowledge is addressed through the outline of the theoretical and methodological contributions as well as social and political implications. Finally, this chapter finishes with an insight into the future development of the multi-agent based model and the suggestions for the further research.

8.2 Reflections on Research Objectives

The research objectives were stated in Chapter 1, and four main objectives were presented in Table 1. An in-depth literature review was conducted in Chapter 2, while research background and critical problems that require further research were addressed in Chapter 3 and 4. This section reflects on the achievements based on the research objectives.

Objective 1: To establish a theoretical framework of knowledge-based innovation by combining the system of innovation theory and the complex adaptive model.

This objective has been achieved through the careful examination of the existing literature on the know-based innovation, the system of innovation and the innovation model. The theoretical framework in this research has advanced the

theoretical framework of knowledge-based innovation from linear, non-linear, network model, to dynamic, self-organized model with the emergent feature.

Objective 2: To identify the dynamics of knowledge through modeling.

An organizational learning model was designed for the purpose of exploring the mechanism of knowledge creation inside the organization and between organizations. The organizational learning model was applied for identifying the dynamics of knowledge in the organizational learning. Moreover, the model examined the influence of different learning strategies and network types on the performance of organizational learning. By analyzing the simulation results, a comprehensive understanding of the dynamics of the knowledge and key issues related to organizational learning were achieved.

Objective 3: To establish a multi-agent based model for simulating knowledge-based innovation at the sectoral level based upon the analysis and findings of biopharmaceutical innovation.

Based on the empirical findings of the dynamics and evolution of knowledge-intensive pharmaceutical innovation, the traditional research methods have been challenged concerning the dynamics of knowledge and the complex network of cooperation. A multi-agent based model, in which there are three main actors (research organizations, biotechnology companies, and big pharmaceutical companies), networks (cooperation), and the environment (public acts), has been established to model the biopharmaceutical innovation. As the innovation process is not a linear development in which the actors are connected to generate new knowledge, the multi-agent based model that breaks down this complicated process based on the knowledge creation and transfer, enables us to explore the biopharmaceutical innovation featured with dynamics, evolution, and adaptiveness. Therefore, the model we presented suited our objective in all respects.

Objective 4: To examine the effectiveness of the ODA through multi-agent based model.

The effectiveness of the ODA has been critically examined through the simulation experiments of how different settings of the ODA incentives influence the orphan drug innovation in the US. The main findings and key issues have been presented in Chapter 6 with the particular focus on the 7-year market exclusivity, which is the most controversial incentive in the ODA.

The research objectives have been achieved in this study by applying social simulation method to the system of innovation theory. The research strategy has provided a rich combination of the empirical data, statistical analysis and simulation findings, all of which have advanced our knowledge about the dynamics of knowledge creation and provided a detailed insight into the influence of the public intervention on the biopharmaceutical innovation.

8.3 The Summary of Findings

According to the boundary, systems of innovation can be classified as national or regional, and it can be sectoral within any of these geographical demarcations. National, regional and sectoral systems of innovation are three variants of the SI approach. The primary research objective of this study is to explore the influence of the ODA on the biopharmaceutical innovation in the US. For this SI, the geographic boundary is the US, and biopharmaceutical industry is the sectoral boundary. SSI is the theory base used to study the dynamics and evolution of this system with its specific knowledge base, products, actors and interactions. Various models have been applied to analyze the SI: linear, non-linear, network and complex system. The system of biopharmaceutical innovation is not a static, straightforward and isolated system. As a result, the

traditional model is too simple to analyze the dynamic, evolutionary and connected SI.

The overall findings suggest that innovation network is not something new, instead the organizational learning should be considered as a strategy for further improving existing knowledge and exploring new knowledge by creating new patterns of inter-organizational interactions. The strategic value of organizational learning is its emphasis on the significance of cooperation between the organizations regarding the learning patterns between exploration and exploitation. Given the main actors and networks addressed within the SSI for generating knowledge-based innovation, the public intervention is a determining factor in influencing the innovation system of a specific sector. The following sections will outline the key findings that have emerged out of the analysis of research outcomes.

8.3.1 Knowledge

One of the objectives of this study is to answer the questions about the evolution of the biopharmaceutical sector and the response of companies to the advancements in science and technology. The concept of a technological regime was applied, and the description of drug innovation period was presented in this study. The technological regime is a combination of knowledge for biopharmaceutical innovation. Different types of knowledge are involved in the R&D of drugs, and lead to two periods of drug innovation. In the “small molecule regime” before 1980, the drug R&D was based on large-scale random screening, and most R&D activities took place in big pharmaceutical companies. In the “biotechnology regime” since 1980, new knowledge generated from the area of molecular biology and genomics has enabled researchers to study the nature of specific diseases, pathophysiology and disease targets, and create possible drug candidates. The new knowledge has been widely spread in research organizations and small biotechnology companies. The differences between the

two technological regimes accounted for the evolution of company business model, which includes the learning strategy and business strategy.

Our study addressed the change of the technology regime and accordingly the evolution of the sector. The largely vertically-integrated pharmaceutical firms dominated the industry, since drug discovery and development are related to “economies of scale and scope, large sunk costs and advantages derived from integrated value chain (Rasmussen 2010)”. The changing of the knowledge base since the 1980s has reshaped the pharmaceutical sector. With the declining productivity of traditional drug pipelines and the expiration of patents, large pharmaceutical companies had to acquire new technology and share the risks through alliances. It is notable that the most successful pharmaceutical companies still retained their large scales and integrated business models, the value of which was not impaired in drug development (clinical trial) and marketing by the impact of biotechnology. But, large pharmaceutical companies looked for new strategies to develop innovative drugs by using latest science and technology to strengthen their positions. They have undertaken joint R&D projects with biotechnology companies through strategic technology agreement, such as joint venture (JV), R&D contracts, R&D agreements, and research contracts.

The sector in the third period is not a number of isolated companies, but rather a complex system with various participants connecting with each other. Companies in the network have strengthened their positions and enhanced their core competencies by accessing complementary knowledge and resources. Companies have gained opportunities to share the risk of development of innovative products and the risk of new emerging market. The complex and costly orphan drug R&D process requires more advanced and strategic relationships with the involvement of patient groups, research originations, FDA authorities, investors and other companies. Nowadays, biopharmaceutical companies have engaged in various alliances with universities and research organizations to reduce R&D costs and risks. Moreover, the cooperation with

patient groups and FDA authorities have contributed to the clinical trials and marketing.

A better understanding of the government actions that have driven the success of orphan drug innovation in the US would be the basis for countries intending to design the legislation. However, simply copying successful stories can hardly lead to another successful story, as even success stories were seldom the same. Governments need to design the S&T institutions and policies according to the historical, political and cultural factors. As 'all roads lead to Rome', governments have considerable freedom to customize national strategies to encourage the orphan drug innovation.

8.3.2 Network

Knowledge is the critical concept of understanding innovation, and learning is the critical concept of the theory of the system of innovation. The idea of learning in the SI approach stresses on the interaction that is the most important locus for innovation. In this study, the knowledge-based view of the firm is selected because it stresses on the micro-level analysis and pays attention to the company's learning activities and interactions. The model we introduced in the thesis enables us to find out how the different patterns of cooperation influence the outcome of innovation.

Our research showed that the inter-organizational learning network can facilitate knowledge flow and creation. There are many factors influencing the innovation activities of companies involved in the network, such as network position, absorptive capacity and network structure (Tsai 2001, Reagans and McEvily 2003). We introduced the concept of exploration and exploitation as explanatory factors underpinning the organizational learning. We studied the performance of companies through different learning strategy settings and found that there were significant differences across companies implementing different strategies. Moreover, the innovation performance of companies was

significantly related to their inter-organizational learning strategies. The results provided suggestions for policy-makers in improving the system of innovation, especially in facilitating and supporting the innovation network.

In the US orphan drug innovation system, the network does not only include research organizations, biotechnology companies, and pharmaceutical companies but also include the NORD, the FDA, and the NIH. As the first and the largest patient organization in the US, the NORD connects the patients, drug developers and authority to facilitate information flow and advance medical research. Patients are willing to contribute to the clinical trial to get access to the latest treatment; while drug developers and FDA look for patients to be enrolled in the drug development process. The NORD is a bridge connecting patients and the industry by establishing the patient database as well as connecting patients to treatments. Although, most of the orphan drug innovation activities are located in the US, there is a trend that the innovation network has been enlarged to the international level in recent years. Some of the orphan drugs approved in the US were developed by foreign companies, and the US companies have sought global resources to enrich their product pipeline. The FDA works closely with industry, patient groups, research organizations and government agencies. By connecting the expertise with drug developers, the uncertainty of clinical trials has been reduced to a lower level. The NIH links patients, the advocacy organization, healthcare professionals and researchers. Through the connections with the NIH, 1) patients can get information about a specific rare disease, such as the latest research and clinical trial; 2) healthcare professionals can acquire timely and reliable information to identify the patient as early as possible and manage the disease in the long-term run; 3) researchers can find disease-specific information including signs and symptoms, incidence, prevalence, funding opportunities, and advocacy organizations that may collaborate with for patient recruitment and patient retention.

To sum up, there is a highly connected and versatile network embedded in the biopharmaceutical innovation. The network has provided the vital information

that includes the essential information about: science and technology, funding, investment opportunities, labor, cooperation, standard, and market. These kinds of information are especially crucial in the knowledge-intensive and capital-intensive sector, like biopharmaceutical sector. The evidence from the ODA suggested that public intervention could solve the market failures that obstruct the innovation, which we will address in the next section. However, the government needs to build and maintain an active network to accelerate the information flow and reduce the cost of communication.

8.3.3 Market Exclusivity as an Incentive to Innovation

The balance between private rights and public interest as well as the balance between innovation and accessibility or affordability are at the center of the present controversy surrounding orphan drugs. There is no doubt that the ODA is a successful public intervention in creating incentives for the companies to develop orphan drugs. The orphan drug was featured as unprofitable due to the small market and huge cost, so there was no opportunity for drug companies to recover their investment costs or even to make a profit. Therefore, the pharmaceutical industry had largely focused on investing in drugs for common diseases. When the market force failed to bring orphan drugs to patients, the public force was required to offer some incentives for companies to invest in orphan drugs. In 1983, the US was the first country to pass the legislative intervention targeting the issue of orphan drugs. In order to encourage the research, development and marketing of orphan drugs, the ODA was designed to offer drug companies the necessary incentives including 7-year market exclusivity, tax credit for clinical testing costs, grants for clinical trials, protocol assistance and open protocols for getting orphan drugs to patients quicker.

Of all the incentives offered by the ODA, the market exclusivity is particularly controversial. The ODA gives the 7-year market exclusivity right for the orphan drug issued market authorization by FDA. Unlike the other incentives that have

been widely accepted by patient groups, drug companies and legislators as fairly successful stimulus, market exclusivity has been considered as the most powerful incentive to attract drug companies. But it is also criticized as an ineffective incentive for the availability of orphan drugs.

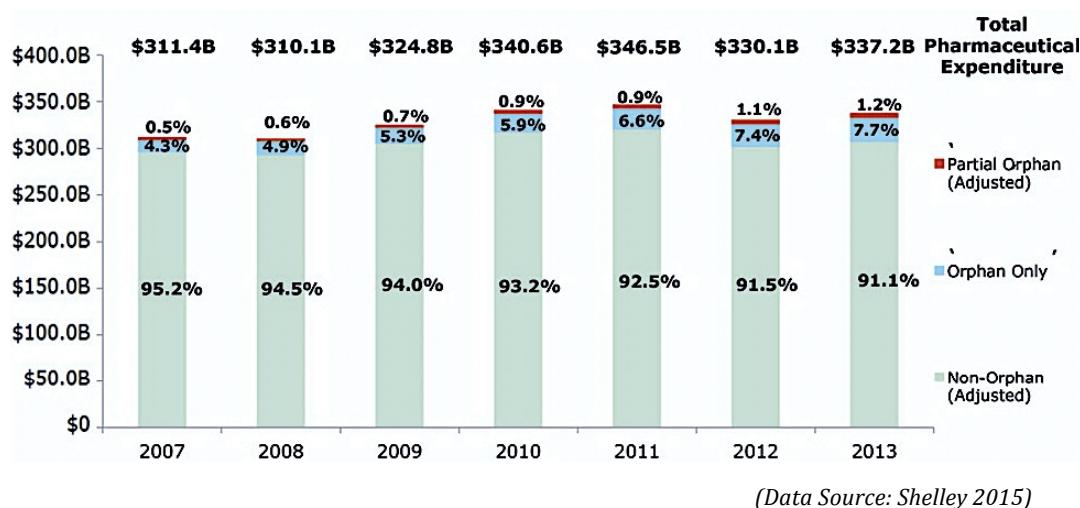


Figure 44 The Growing Proportion of The US Orphan Drug Expenditure

The market exclusivity is different from the patent which is the normal way to protect the interests of the inventor by excluding others from making, using or selling an invention for a limited time. Regarding drugs, patents are granted by the patent and trademark office at any time during the development lifeline of a drug. Patents expire 20 years from the date of filing, and it is highly possible that they can expire even before drug approval. Exclusivity works in a similar way with patent, but it is granted by FDA upon the approval of a drug, and it provides 7-year market protection for the orphan drug.

Orphan drugs are generally very expensive, with some drugs costing from \$200,000 to \$300,000 per patient per year, and treatments usually last for a patient's lifetime. Despite the high price, payers have little scrutiny on the coverage because of the high unmet need of rare disease patients and the relatively small proportion of the total budget for any given payer or health plans (the small number of patients). In recent years, the expenditure of orphan drugs accounts for nearly 10% of the total pharmaceutical expenditure (Figure

44). With the increasing number of orphan drugs in the market, the aggregate budget impact for many payers has grown, and the payers' attitudes towards orphan drug are changing. They are starting to increase the scrutiny of the pricing and the reimbursement, and to consider the options such as sharing the cost with patients or step-therapy protocols to control the escalating costs, but this will lead to the concerns from patients and drug providers.

The primary objective of the ODA is to increase the number of drugs available to patients with rare diseases. Based on this criterion, the ODA might be considered a success, as most evident from the difference in the number of approved orphan drugs before and after ODA. From the simulation results, we could see the market exclusivity had a significant influence on the number of authorized orphan drugs. The cancellation of market exclusivity would totally change the current prosperity of the orphan drug innovation, and shortening the duration of market exclusivity would only lead to a risky situation of orphan drug innovation. Although market exclusivity has generated positive outcomes, its misuse could lead to the improper benefits of drug companies at the cost of patients and public.

The research results suggested that the incentives should be designed and implemented in a way that can make much attention to the fairness and the sustainability. Alternative methods should be considered for resolving the exposed problems of the ODA. First of all, it is essential that these methods should be based on the balance between public and private interests. The proposed solutions include the reduced exclusivity period once the use of drugs extended to other diseases or the return of a reasonable rate of profit to the government if an orphan drug is exceptionally profitable. Despite the significant progress the ODA has made, much work remains to be done. Around 7000 rare diseases have already been identified, and many of them are with the high mortality rate, but only 5% of them have the approved therapy for the patients. Another way of encouraging the innovation without taking the undue advantage of the ODA is to increase the direct funding support to encourage the basic

research and to conduct the costly clinical trials for the neglected rare diseases. In all, the effective incentives should be tied more closely to the improvement of the health outcomes of the patients suffering from rare diseases.

The US ODA has set a good example for other countries to design the public interventions for orphan drug innovation. Our analysis of the ODA has achieved a comprehensive understanding of the orphan drug legislation and how it works in the pharmaceutical innovation system, which would assist the policy-makers to make orphan drug legislations based on different national conditions.

8.3.4 Summary

This thesis started with an overview of the shift of the model of innovation from linear towards the complex adaptive model as a result of the in-depth understanding of the SI. An increasing attention has been paid to the network of innovation that plays a vital role in generating new knowledge. However, moving to the new model of innovation requires developing a new method to understand the dynamics involved in creating knowledge-based innovation. The dynamics involved in the knowledge network, in addition, the micro and social process of analysis of knowledge creation through exploration and exploitation complemented the existing study on knowledge-based innovation theory.

In conclusion, this section has succeeded in addressing the critical problems emerging from the ODA, which is closely related to the effective implementation of the complex adaptive system model of knowledge-based innovation. The complex adaptive system was still at the conceptual or theoretical level to analyze the innovation. There was little attention paid to the implementation of the complex adaptive model both at the micro level and the strategy and policy intention at the macro level. In the light of the analysis within the thesis, although CAS model is complex and dynamic, the process of innovation in the complex adaptive system can be managed. The effectiveness of the knowledge-

based innovation requires developing the appropriate strategy for companies in the network.

8.4 Contribution to Knowledge

The literature from the research of the SI indicated that the current research method of the SI was facing challenges in practice and needed to employ a different method. Complex adaptive system, as a heuristic concept from the area of natural science, has undoubtedly offered a valuable framework that reinforces our understanding of the knowledge-intensive innovation system. The distinctness of this research lies in to enrich the existing theories of the SI by highlighting the network, complexity, adaptiveness, emergent feature and public intervention. This could enable researchers, innovation actors and policy-makers to think beyond the preceding model, by taking into the consideration of the dynamics of organizational learning and the complicated networking process. The research findings have significant implications for government policy-makers and research academics in addressing the existing deficiencies in the implement of the knowledge-based innovation strategies.

8.4.1 Theoretical Contribution

Overall, the research has expanded the theory of the SI in terms of emphasizing on the dynamics and complexity of the system and made a step forward in developing the complex adaptive model of innovation in the following ways.

- Firstly, organizational learning has been paid considerable attention, and it has been addressed by a wide range of research, for instance, organizational theory, economics, and innovation studies. Although some researchers have discussed the difference between exploration and exploitation and paid attention to the relationships between them, our

understanding of the interactions between both activities and how they work together in the SI remained rather unclear. This research has extended the current work by addressing the dynamic learning process at the intra-organization and inter-organization level in terms of exploration and exploitation, and by examining the ways in which organizational learning may be facilitated through balancing exploration and exploitation. Furthermore, this study has moved beyond the conceptual model and examined our assumptions about organizational learning by social simulation. Through our findings, the research has provided a clearer understanding of how organizations coordinate the exploration and exploitation in organizational units or in the network to achieve success.

- The second theoretical contribution of this research lay in updating the theoretical foundation of the SI from the linear, non-linear and network view of innovation to a complex systematic viewpoint. The linear, non-linear and network models were three main innovation models dominating the past and current innovation research, the features and shortcomings of them have been identified after reviewing its main concepts in Chapter 2, and it was argued that the further development and extension of the SI theory is very much needed as the systems have become more and more complex, particularly when it is going to be applied in the knowledge-intensive systems of innovation (Figure 45). This study has adopted the complex adaptive system in the theory construction. We advanced the growing amount of the literature focusing on the complexity of the SI by employing CAS to show the dynamics, evolution, and adaptiveness of the system.

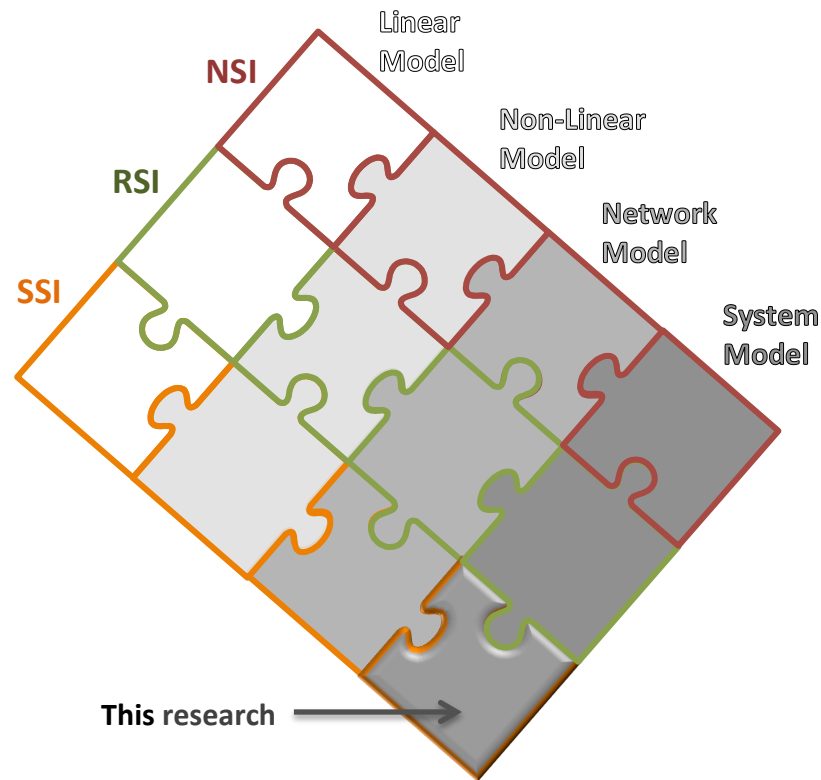


Figure 45 The Theory Mapping of Innovation

- The third noteworthy theoretical contribution of this research was the attention paid to the sectoral system of innovation. Although the system of innovation is at the center of the innovation study, sectoral system of innovation is rather new and has not yet attracted sufficient attention from scholars. Different from the previous research on the SSI, in this research, SSI was considered as a complex adaptive system, in which various actors were modeled as heterogeneous agents; the relationships were modeled as the network; and the public intervention was modeled as the environment. This distinction not only strengthens the SSI theory on its account of the system dynamics but also extends its applicability to analyzing the policy implication.

8.4.2 Methodological Implications

All the research results heavily rely on the methodology of the agent-based simulation. Social simulation and computational model like multi-agent based models have shown to be highly suitable for the study of the complex adaptive model of innovation. Computational modeling has been applied in many other fields to present complex adaptive system and to explore the mechanisms that drive their evolution over time. For the social research, such models are still rare, but there are signs that indicate this is going to change. Because the social simulation has allowed us to gain different knowledge compared with traditional research methods. In this section, the advantages and challenges related to the simulation are summarized.

Regarding the methodological part of this study, three remarks have been made. Firstly, this study made an important step to simulate the pharmaceutical innovation process from drug discovery, drug development to drug commercialization. Secondly, in addition to the first remark, we also made the innovation process tangible in terms of knowledge. We measured the generation of knowledge within different organizational learning strategies. And finally, this research provided insights into modeling network dynamics in the SI. The model can be considered as a powerful tool for future research, and it has the potential to generate more insights.

To deal with the complex adaptive system of innovation requires a different way of thinking: focusing on the system as a whole, including all the actors and the structure of their interactions over time and considering the dynamic nature and the emergent feature. The various cooperation in the network together with the dynamics posed a challenge to the traditional research methods. In the research of the SI with intense interactions, the networks are too complicated to solve them analytically and therefore computational experiment is a suitable research method to understand how the system works and to do the what-if experiments which cannot be done in the real world to explore how different

settings of model's parameters influencing system's output. In the multi-agent based model, the real world is created and populated by agents that are able to make their own decisions and to act and interact with other actors autonomously following their own strategies and interests. The agents are simulated as actual individual or organization, and the agent-based model is simulated as a social system with emergent phenomena. Compared with the previous linear, non-linear and network model, CAS model is an advanced model of the system of innovation in terms of heterogeneous agents, dynamic learning process, network formation, adaptiveness, and self-organization.

The validation of the model was undertaken on the basis of empirical experiments about the past decades of orphan drug innovation. The first several experiments showed that our model was history-friendly and the results were highly related to the historical data. At the same time, it was demonstrated that this model could reproduce the entire range of patterns of behavior that exist in the real orphan drug innovation system. Furthermore, with the same model but different combinations of parameters the model generated the outcomes that not only explained some features of innovation system but also answered some what-if questions allowing us to improve the understanding of the system.

In this research, we have also experienced some challenges when building the model. The multi-agent based model can be designed too large or too complex to be interpreted. Although the more information the model synthesizes, the more accurate the model is. However, any model is not able to reproduce the world as exactly the same as in the reality. Hence, balancing the complexity of the model with its capacity to describe the phenomenon we're interested in is the most critical factor of modeling. Having a descriptive model is the key step for all the social simulation before building the computational model.

Our model is the result of many hard works, but it is only at an early stage in the development of models of the complex innovation system, and of course, it's not perfect. There are some aspects that could be improved or implemented

differently. The multi-agent based simulation has been used in many research areas, but these research exist a common problem especially in the social study. The problem is the empirical foundations of these models are usually missing or weak. This can be caused by the data we are interested in is very hard to get, or the data doesn't exist in the real world. The micro specification of these data in the model is often inspired by the intuition of the modelers (Epstein 1999). Although the lack of empirical foundation doesn't represent a limitation, the models would achieve a substantial academic value if they could be supported by robust empirical data. In this research, a number of empirical data have been applied to assist our modeling, but there are still some data missing because of the impossibility and impediment of data collection. Without regard to the difficulty of data collection, it's believed that if all the input parameters can be guided by the empirical data that may considerably contribute to the reputation of the multi-agent based model.

8.4.3 Practical Contribution and Policy Implication

This study has contributed to the knowledge-based system of innovation on how to develop effective innovation networks and design effective sectoral innovation policy. It has focused on the process of knowledge creation based on the exploration and the exploitation through interactive innovation networks. A model was developed to simulate the knowledge creation at the sector level. In this research, the sector is very unique: it is a knowledge-intensive sector but the market is too small to attract companies to develop the product, but public interventions successfully boost the innovation of this sector. The model helped us to understand the process of knowledge creation in biopharmaceutical sector and provide rich insights on designing innovation policy for the orphan drug innovation.

There have been many discussions on how to create an effective knowledge-based system of innovation at the macro-level, but there has been lack of the empirical and practical research at the micro-level on explaining how the

innovation networks are formed, evolved and operated to create competitive advantages for actors in the network and to influence the performance of the whole network. The outcome of this research revealed how innovation capability is enhanced through the dynamic interactive process between actors. The research also has the enlightening influence upon academic researchers, managers, intermediaries, and policy-makers with interests in managing effective implement of knowledge-based innovation policy at the sector level.

The system of innovation in the orphan drug sector is a unique social, economic, political and historical context. A sustainable future for both rare disease treatment and healthcare system requires that we do not analyze the different parts of the sector separately rather than consider them as a whole system. This research unraveled the internal dynamics of the biopharmaceutical industry and attempted to examine the most controversial incentive to seek the best trade-off between quantity and price. The interconnections between pharmaceutical developments, pharmaceutical policy, and innovation theories helped us to understand how they shape the current situation of orphan drug innovation. The findings from the thesis provided companies with a deeper understanding of managing the dynamic interactive innovation process within the network and provided policy-makers with the enlightened thinking of developing innovation policies that could balance social welfare with economic benefits.

From policy perspectives, there are a number of implications for policymakers to design innovation policies stimulating sectoral innovation, especially for the sector when the small market fails to attract firms to develop products. Firstly, ensuring the profits of companies is the most powerful tool to attract companies to enter into the sector. Protecting the intellectual property is of particular importance for the knowledge-intensive sector, and when the patent legislation is not applicable for the products in the industry giving the market right for companies is a way to secure their income. Secondly, gaining access to regulatory experts is particularly important, because such access can help drug

companies to design the most appropriate clinical trial by avoiding pitfalls and obstacles in the drug development process, and it can lead to a timely and successful drug approval. The least but the most important, the advance of science and technology is the precondition for the innovation, without the significant improvement of basic research in the area of biotechnology, the orphan drug innovation cannot be triggered even it's lured by market right. Although pharmaceutical industry provides an enormous amount of the funds for R&D, the basic research is largely funded by the public sector. Most of the basic biomedical research are supported by the National Institute of Health (NIH) (Moses, Dorsey et al. 2005). The public funding from government has played an indirect role by funding basic research that is the foundation of drug discovery process.

Based on the analysis in Chapter 6, it's clear that the ODA is successful in promoting the innovation of not only orphan drugs but also other biotechnology drugs. Innovation policy needs to focus on developing more robust and endogenous innovative ability for knowledge-base innovation through concentrated action on supporting and managing the key issues that have been raised during the R&D process in an appropriate and effective manner. As the most controversial incentive, market exclusivity has played an important role in the prosperity of orphan drug innovation; at the same time, the high costs of some rare disease treatments have made it at the center of controversy. From the simulation results, we can see shortening the duration of market exclusivity is not a reasonable method to avoid the blockbuster orphan drug as drug companies are very sensitive to the issue, the best way to solve this problem is to enact the multi-tier policy for the blockbuster orphan drug and repurposed orphan drug.

The contributions from the case study based on a unique sector in a unique country, unavoidably bear many exceptions. It's very dangerous to simply copy the US policy to other countries. The uniqueness of the success of the ODA could be found in its national context (US), its specific industry, and its science and

technology background within that period. But it could shed light on many other countries planning to make the policies about orphan drug or even other products of which the market is not strong enough to stimulate the companies to produce the products.

8.5 Recommendations for Further Research

Firms and governments are continuously seeking new ways to improve and develop competence in order to succeed in the global market. It is increasingly accepted that the core of innovation is the creation of knowledge. The strategy and environment in which it is implemented play a prominent role in generating new knowledge.

The findings from our research have left two critical issues for innovation researchers and policymakers: firstly, regarding how to future develop the model to meet different research objectives, and secondly on how to design the innovation policy to stimulate sectoral innovation without misuses. The remainder of this section will introduce several potential directions of further research that would help to tackle the two critical issues above.

There is no doubt that market exclusivity is the most powerful incentives for the orphan drug innovation, where the market fails to drive the R&D. Moreover, it also proves that the patent is an effective incentive for most of the high-tech products. Some of the orphan drugs own the patent and enjoy the 7-year market exclusivity. Nevertheless, the market exclusivity and the patent need to be read with cautions, because they are actually two different concepts. An area of future research could be to explore the different effects of patent and market exclusivity on orphan drugs innovation.

Moreover, the process of drug innovation has been only partly considered in this study. The innovation process in our research includes drug discovery, development and commercialization. The former two processes were fully considered and discussed compared with the last process. This, in turn, was mainly a result of the reality and the objective of the research. Firstly, our research objective is to explore the innovation of orphan drug, so the R&D process is undoubtedly our research priority. Secondly, it's hard to get the detailed information about the drug commercialization, as most of them are considered business secrets. Limited attention has been paid to drug commercialization, and thus further updating could be added to the model in the research focusing on the drug marketing.

Within the scope of this thesis, it is only possible to present the theatrical foundation of the model and exhibit the capabilities of this model in selected settings. Further applications will be part of the future research, especially because the model requires a solid basis of data describing the concrete system. There is still a lot that can be done, but the fundamental research presented here will hopefully serve as a stepping stone that backs the application of agent-based modeling in innovation system research in the future.

8.5.1 ABS Model

The current version of the model still leaves room for exploration and experimentation. The consequent analysis discussed in the research may only scratch part of the wide range of possibilities produced by the complex adaptive system and multi-agent modeling. Much is still to be learnt about the influence of the different combination of network locations (structures) and the learning strategies on the performance of companies. Of special interest is the reproduction of the innovation system of other sectors based on empirical data.

Another type of experiment that could be run directly with the current version of the model is to explore the effects of the network in agent populations

regarding the parameters that control their cooperation activities. In the preceding experiments, the activities of networking were all for the entire population. If possible, such a computational model would be designed in conjunction with empirical data. Designing a sensible combination of heterogeneous agents for the computation model to capture distinct characteristics of organizations in the SI can be very challenging, but if such a setting were calibrated to empirical data, it would constitute another strong foundation for the validity of this model.

In our model, the spatial distribution of the agents was neglected. However, research has shown that the distance between participants in the network influences the likelihood of cooperation independent of other factors. It is possible to include actual physical distance, such as a map of a nation or region, to capture the features of the geographic distributions of agents in the SI. This could be an extension of the current model.

At this stage, the model has simulated the organizational learning by Genetic Algorithms. One more possible area of future research is to explore the variations of the management skills. In the current model, the agents were set up with heterogeneous learning capabilities, and these capabilities allowed the agents to learn internally and externally to develop new drugs. However, this setting ignores the management skills that could influence the companies' innovation activities and outputs. The model would probably be more powerful if more detailed data about companies' management behaviors can be included, but in this research, the constraints posed by confidentiality for access to companies' data has precluded modeling the management behavior.

8.5.2 The Orphan Drug Act

Before the ODA was introduced, the orphan drug was considered as an entirely unprofitable product. Another reason for the lack of orphan drug R&D was the high cost incurred in developing and marketing new drugs. Similar to the

orphan drugs which are developed for the diseases with a small number of patients in the developed countries, neglected drugs developed for the diseases which are almost suffered by patients in the developing countries are believed unprofitable to attract drug manufacturers. The public intervention is necessary to offer some incentives for companies to invest in the drugs for neglected diseases. The public invention of orphan drug R&D was discussed in this research, and further work can be extended to the area of neglected diseases.

The US is the first country to pass orphan drug legislation. Its success inspired the EU, Japan, Singapore, Canada and Australia to enact similar legislation. The model can be extended to represent the orphan drug innovation systems in other countries, and it can help these countries to get a better understanding of the influence of orphan drug legislation on the drug innovation system and to improve the current situation. In addition, the model can be extended to the countries planning to pass orphan drug legislation with the aim of designing incentives according to different national conditions.

As the ODA has been designed for stimulating orphan drug R&D, this research was conducted after the first 30-year implementation. Since 1983, the ODA has been amended continuously, while the orphan drug R&D and market have evolved dramatically. The current R&D and market environment have changed over the past two decades. It is not surprising that the orphan drug is no longer considered as unprofitable. Instead, it is viewed as a huge commercial opportunity for drug companies (Wellman-Labadie and Zhou 2010). According to the orphan drug report from EvaluatePharma (Hadjivasiliou 2015), the sales of orphan drugs has increased from around \$20 billion in 2000 to about \$100 billion in 2015, and it is projected to reach \$180 billion and make up 20.2% of prescription drug sales by 2020. The orphan drug innovation has moved to another phase, in which the orphan drug is never a neglected market. Drug companies have started to pay attention to this promising market. Since the environment is entirely different, rather than sticking onto the current intervention, the change of incentives should be considered in the US. The

future research can be extended to explore the ODA based on the new situation of orphan drug innovation. From our research, it's obvious that the market exclusivity incentive is an important determinant in promoting orphan drug innovation, future amendments in the US should be made more carefully in avoiding misuse and linking to the positive improvement of health outcomes.

8.6 Final Remarks

The research on the SSI based on a country, inevitably, bears some exceptions. For example, the outcomes may have specific role in tackling the controversy surrounding the ODA and improve the ODA to meet every participant's need in the system. Moreover, the outcomes may shed light on the intentions to make orphan drug legislation in many less-developed countries.

It is possible that orphan drug legislation could be an essential condition for stimulating orphan drug innovation. Moreover, orphan drug legislation has been proven to make big scientific and economic contributions to the biopharmaceutical sector. However, this needs to be read with caution because besides the ODA, there are other contributory factors to orphan drug development. For example, the National Organization for Rare Disorders (NORD) promoted awareness of rare diseases among public and professional audience; established the rare disease database and rare action network; and provided grants for basic and translational research. The Office of Orphan Products Development (OOPD) facilitated the flow of information among patients, research organizations, government agencies, and industry. The OORPD also supported the development of orphan drugs by providing grants and professional advice. Getting access to the regulatory experts is very important because it can help companies design the clinical trials and avoid potential obstacles. These factors should not be neglected when designing a new orphan drug legislation.

The development of science and technology is the foundation of the orphan drug innovation. Without its advance, even the powerful market exclusivity seems less functional in generating new orphan drugs. The governments in less-developed countries should take 'science and technology' factors into consideration when embarking on their own legislation project. The legislation would focus on funding the basic research and facilitating the knowledge transfer and creation within the sector. The policy-maker should make an integrated and coherent policy framework, while supporting the sector to coordinate with various other participants in the system.

Appendices

APPENDIX (A) The Modeling Software: Swarm

Stable Release

Swarm 2.2, released in February 2005, is the latest version. This release adds a number of new capabilities and optimizes some components since the previous version Swarm 2.1.1, which was released in April 2000. Swarm software contains a package of code library that enables users to write code in Objective C or Java computer language. Before Swarm 2.0, Objective C is the only way to write and compile Swam program. Since Swarm 2.0, modelers can build models in Java.

Swarm Program

Swarm is designed to build the multi-agent-based model. Researchers need to provide contents and set activity schedules to agents through programing. Object-Oriented programming (OOP) is ideally suited to create the Swarm model. Objective C and Java Object are two of the most popular oriented programs, and both share the same two features:

Encapsulation Object is a self-contained entity, and other objects cannot get access to the information inside this object without the permit. Users only have to know the interface of an object and do not need to know the details of what happens inside each object.

Inheritance Each class in the program is designated to a subclass within an over-arching superclass, all variables and methods of each subclass are inherited from its superclass. Subclass not only inherits a base of all variables and methods of the superclass but also can add new variables and methods.

The Components of Swarm Simulation

The Swarm simulation is built on the concept of Swarm. Swarms are the fundamental 'building blocks' in Swarm application. A swarm contains a collection of objects and a

schedule of objects' activities.

1) Object

The core aim of Swarm is to make an execution context within which a large number of objects can behave in a distributed manner. Building Swarm model is by means of incorporating Swarm objects in program. A typical object consists of two types of information: variables defining the 'state' of object and methods determining the activities of objects.

The states of the object vary according to different models, for instance, the age, type, wealth, ability of the object and so forth. In the orphan drug innovation model, the objects are the various organizations including small biotechnology companies, big pharmaceutical companies and so on; the states of objects include the size, type, innovation ability and cooperation strategy of these organizations. States are represented as variables in program. All of this information is encapsulated in objects, and they are available to all methods inside this object.

Methods are designed to receive information from the outside and convey messages to the outside. They are usually interpreted as functions that describe how objects respond to changes in its state and input or interaction with other objects. Methods are also used to retain categorize and summarize the information.

In Swarm, objects are created by *buildobjects* method. *Buildobjects* not only creates objects in the current class but also manages the object creation in the next lower level. For example, in observer swarm, *buildobjectcs* creates objects for graphical display, control panel and next-lower level object - model swarm.

Table 30 The Mapping from Model to Swarm

Model	Swarm Implementation
Agents	Objects
Events	Messages
Observations	Display Objects
Instruments and Probes	Probe Objects
Statistical Tools	Analysis Objects

2) Schedule

The actions of objects are implemented by objects responding to their schedules. The schedule provides a way to integrate the actions and a number of various objects in the different level of simulation. It is like a clock controlling when the actions are supposed to occur.

A Swarm model runs in discrete time steps. To manage agents' behavior, interaction and time sequences, Swarm model has two methods. The *buildobjects* method creates objects and *buildactions* creates schedules. *Buildobjects* method creates the objects in current class and lower level class. *Buildactions* method creates two classes: *Actiongroup* creates an ordered set of events, *Schedule* controls the frequency of the events executed in the *Actiongroup*. The *buildactions* method first creates an *Actiongroup*, which includes a collection of actions that happen in certain sequence, and then controls these actions perform in certain frequency.

Since *buildactions* methods can be used in different classes, each class can create their *Actiongroups* and *Schedules*, to coordinate all these activities logistically is very important. The schedule of each swarm is merged into the schedule of next higher-level swarm and finally merged into the top-level swarm. This multi-level integration of swarm schedule indicates that the model can be thought as a structure of hierarchy.

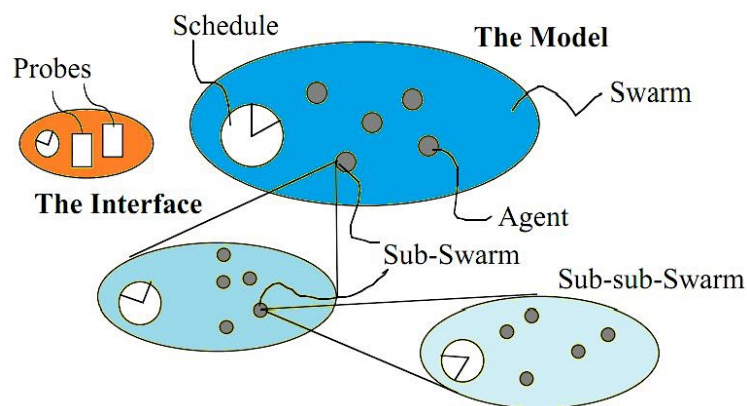


Figure 46 The Hierarchy of Swarm

The Structure of Swarm Simulation

The Swarm structure has two levels: the model level and observer level.

1) Model Swarm

Model swarm is the core of Swarm simulation. It encapsulates the objects and their activities in the simulated model. It creates the objects correspond to the world we model, schedules their activities and shows the effects of passing time on the model. Model swarm contains a set of inputs used to set the parameters and outputs used to collect and relay information when the observer swarm needs them.

2) Observer Swarm

Besides the objects simulated, Swarm model also includes the experimental apparatus used for observation and measurement. Observer Swarm is the top-level Swarm in a Swarm model, and it has a collection of objects among which Model Swarm is one of the most essential objects. Other objects in Observer Swarm are used to obtain data from Model Swarm and send the output data to various display tools and widgets.

APPENDIX (B) The Modeling Software: NetLogo

The Stable Release

The first version of NetLogo Version 1.0 was released on April 2002. Since that time, it has been developed continuously. The Latest version of NetLogo is Version 5.2.1 that is released on September 2015. It has an extensive model library including models from economics, biology, physics, chemistry, phycology, and system dynamics.

NetLogo Programme

NetLogo is a high-level platform. It has a simple but powerful programming language, built-in graphical interfaces and comprehensive documentation (Allan 2009). Its programming includes many high-level structures and primitives that make the programming easier. NetLogo has switches, sliders, choosers, inputs and other interface elements, which make the software user-friendly.

An important feature of NetLogo, not found in other ABSTs, is the ‘agentsets’. The ‘agentsets’ is a set of agents, which can all be turtles or patches, and it can be customized with specific characteristics. It is very useful when giving certain instructions to. The agents are responsible for the majority of NetLogo’s expressive power. Another important feature of NetLogo is that results can be scientifically reproducible so that the models are able to operate deterministically. That means when the modeler sets the random number generator the same way, NetLogo always follows the same routines in the same way and generates the same results.

Installation

The NetLogo can be run on most systems, including Windows, Mac OS X, Linux and other systems. The software is free, and it can be download from <https://ccl.northwestern.edu/netlogo/download.shtml>. It is open source software; the source code is stored at <https://github.com/NetLogo/NetLogo>.

The Components of NetLogo

The general principles of NetLogo modeling take the following forms: creating an artificial world filled with turtles, patches, and links. The NetLogo world is a two-dimensional world that is composed of turtles, patches, links, and an observer, all of which are agents in the model. The patches are the ground over which the turtles move. Links are connections between turtles. The observer oversees everything that is going on and does whatever the turtles, patches, and links cannot do for themselves. All four types of agents can run NetLogo commands and procedures that are a series of commands integrated into a single new command.

Table 31 The Terminology Difference between NetLogo and Swarm

Term/Concept	NetLogo	Swarm
The object that builds and controls simulation objects	Observer	modelswarm
The object that builds and controls graphing	Interface	Observer swarm
The object that represents space and agent location	World	Space
The object that represents the agents	Turtle	swarm
Agent's behavior or activity	procedure	action
Agent's activities	Forever procedure	schedule
Display of data	Monitor	Probe display

The Structure of NetLogo

The concept of NetLogo can be compared to 'turtles' that move around and interact with each other on 'patches'. In the model, there can be thousands of 'turtles', which come from different 'breeds'. The patches are portrayed as a lattice in some models, like in cellular automata; they can also be square sections of a continuous two-dimensional space. Both 'turtles' and 'patches' are agents, and they are controlled by an 'observer'. There is only one observer in the model, and it keeps the model working by giving instructions to 'turtles' and 'patches'.

APPENDIX (C) The Explanation of The Prevalence PVL

The rare disease is defined as any disease or condition that affects fewer than 200,000 people in the United States. The prevalence PVL_n refers to the number of the cases of the rare disease n in the US population. In the model, the PVL_n follows the uniform distribution over the interval $[1, 200000]$.

PVL is further standardized as PVL^* , which is uniformly distributed over $[0.000005, 1]$. As shown in Figure 47, $-5.3 \leq Lg(PVL^*) \leq 0$.

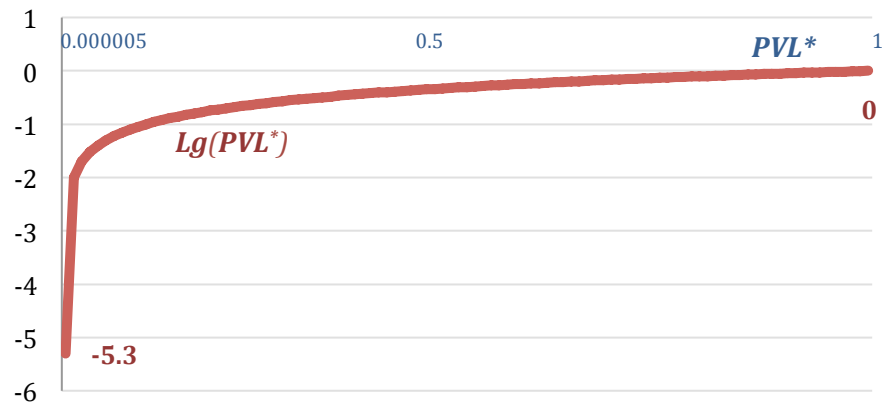


Figure 47 The Graph of $Lg(PVL^*)$

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